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Synthesis of Z-Protected Aib- and Phe(2Me)-Containing Pentapeptides and Their Crystal Structures

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A series of pentapeptide derivatives containing α,α-disubstituted α-amino acids have been prepared by a combination of the 'azirine/oxazolone method' and segment condensations. X-ray crystal-structure determinations of the molecular structures confirmed the presence of helical conformations stabilized by β-turns of type III or III'. Pentapeptides containing (*R*)-Phe(2Me) form a right-handed helix, whereas those containing (*S*)-Phe(2Me) adopt a left-handed helical structure.

1. Introduction. – Since the elaboration of the 'azirine/oxazolone method' as a convenient protocol for the synthesis of Aib-containing peptides [1–3], this procedure has been used successfully for the preparation of model peptides [2c][3–6], sterically congested oligopeptides [7][8], and peptaibols [2d][9–11]. It has also been shown that the method can be adopted to solid-phase methodology [12]. Another modification allowed the synthesis of endothiopeptides containing Aib units [13–16].

In the present study, a series of Z-protected pentapeptides containing α,α-disubstituted α-amino acids were prepared according to this method. All α,α-disubstituted α-amino acids were introduced *via* coupling of amino or peptide acids with 2,2-disubstituted 2*H*-azirin-3-amines. The synthon for Phe(2Me) was the racemic 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine leading to mixtures of (*R*)- and (*S*)-Phe(2Me)-peptides[2]). In the case of diastereoisomers, they were separated chromatographically.

Based on the studies of *Ramachandran et al.* [18] it is well-known that the introduction of α,α-disubstituted α-amino acids[3] into peptides stabilizes β-turn and 3_{10}-helical conformations [19][20]. For the crystalline state, this has been proven by X-ray crystallography (*e.g.*, [21][22]). In spite of this knowledge, current interest in conformations of small peptides is documented by several recent reports (*e.g.*, for pentapeptides [23][24]). For this reason, we determined the crystal structures of some of the prepared pentapeptides.

2. Results and Discussion. – 2.1. *Synthesis of Pentapeptides*. The syntheses of the Z-protected pentapeptides were carried out *via* combinations of the coupling of amino or peptide acids with 2*H*-azirin-3-amines and standard coupling with amino acid esters or peptide

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[2]) Synthons for enantiomerically pure (*R*)- and (*S*)-Phe(2Me) are now also available [4a][17].

[3]) The prototype is α-aminoisobutyric acid (Aib).

segments. Two examples are shown in *Scheme 1*: Following the procedure described in [11][25], Z-Gly-OH in THF was reacted with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**, Aib synthon [26]) leading to dipeptide amide **2**, followed by selective hydrolysis to give Z-Gly-Aib-OH (**3**). Reaction of the latter with 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1b**) [26b] yielded the tripeptide amide **4a** [25a], which was hydrolyzed (→ **5a**), coupled with **1a** (→ **6a**) and again hydrolyzed (→ **7a**). The coupling of **7a** with H-Gly-OMe and H-Phe-OBn, respectively, was carried out in CH_2Cl_2 using PyBOP/DIEA[4]) as the coupling reagent, leading to pentapeptide **8a**[5]) and **8b**, respectively. The latter was obtained as a 1:1 mixture of diastereoisomers.

Scheme 1

Similar to the preparation of **8a** and **8b**, pentapeptide **8c** containing 1-aminocyclobutane carboxylic acid (Acb) was synthesized (*Scheme 2*). Coupling of **3** with 2-(*N*,*N*-dimethylamino)-1-azaspiro[2.3]hex-1-ene (**1c**) [2b] gave the tripeptide amide **4b** in 87% yield. The hydrolysis of the terminal amide group was achieved in 3N HCl (THF/H_2O) at 40° leading to **5b** (96%). Subsequent azirine coupling with **1a** (→ **6b**), selective hydrolysis at room temperature (→ **7b**), and coupling with H-Gly-OMe by treatment with PyBOP/DIEA gave **8c**.

Scheme 2

[4]) PyBOP = [(Benzotriazol-1-yl)oxy]tripyrrolidinophosphonium hexafluorophosphate; DIEA = ethyl(diisopropyl)amine (*Hünig* base).

[5]) The coupling of **7** with H-Gly-OMe was also achieved by treatment with DCC, $ZnCl_2$, and Et_3N in DMF [27][28] leading to **8a** in 70% yield.

The Pro-containing pentapeptide **8d** was obtained by segment coupling of **3** and H-Pro-Aib-Aib-N(Me)Ph (**9**) in CH_2Cl_2 with HBPyU/DIEA[6]) as the coupling reagent [29] (*Scheme 3*). The tripeptide **9** [25b] was prepared by subsequent coupling of Z-Pro-OH with azirine **1a**, selective hydrolysis, again coupling with **1a**, and deprotection of the *N*-terminus by hydrogenolysis. Selective hydrolysis of **8d** under the usual conditions gave the pentapeptide acid **10** in 70% yield.

Scheme 3

The pentapeptides **8e** and **8f** were prepared *via* coupling of the dipeptide segment **11** [25a] with the tripeptide segment **12** and the corresponding H-Gly-Aib-Aib-N(Me)Ph [25a], respectively (*Scheme 4*). The coupling was performed by treatment with PyBOP/DIEA in CH_2Cl_2 at room temperature and led to **8e** as a 1:1 mixture of diastereoisomers in almost quantitative yield. The corresponding **8f** was isolated in 82% yield as a racemate. The segment **12** was obtained by coupling of **3** with H-Phe-OMe (PyBOP/DIEA; 85%), followed by hydrogenolytic deprotection of the NH_2 group (98%). The diastereoisomers of **8e** were separated chromatographically (SiO_2, AcOEt/MeOH), and the pure isomers were isolated in 47% ((*S*,*S*)-**8e**) and 44% ((*R*,*S*)-**8e**) yield. The configuration of (*S*,*S*)-**8e** was determined by X-ray crystallography (see chapter 2.3).

Scheme 4

[6]) HBPyU = *O*-[(Benzotriazol-1-yl)oxy]dipyrrolidinocarbenium hexafluorophosphate.

Finally, the dipeptide segment **11** was coupled with the tripeptides H-Pro-Aib-Phe-OMe (**13**) and the corresponding H-Pro-Aib-Aib-N(Me)Ph [25b], respectively, leading to pentapeptides **8g** and **8h** (*Scheme 5*). These couplings proved to be rather difficult. In the case of **8g**, the reaction with PyBOP/DIEA in CH_2Cl_2 for 19.5 h gave the product in only 39% yield, whereas with TBTU/HOBt/DIEA[7]), after 19.5 h, **8g** was isolated in 74% yield. Also in the case of **8h**, TBTU/HOBt gave slightly better results than PyBOP/DIEA. The tripeptide **13** was prepared by coupling of Z-Pro-Aib-OH [25b] with H-Phe-OMe by treatment with PyBOP/DIEA.

Scheme 5

In both cases, **8g** and **8h**, mixtures of diastereoisomers were formed, which could be separated by column chromatography (SiO_2, AcOEt/MeOH). The pure epimers (*R*,*S*,*S*)-**8g** and (*S*,*S*,*S*)-**8g** were obtained in a 1.6:1 ratio[8]). As the starting dipeptide **11** is a racemate, the coupling of (*R*)-**11** with **13** is obviously more efficient than that of (*S*)-**11**. A similar result was obtained in the case of **8h**: the epimers (*R*,*S*)-**8h** and (*S*,*S*)-**8h**[8]) were obtained in a 2:1 ratio.

2.2. *Conformation of the Pro-Peptide Bonds in the Pentapeptides in Solution.* – Whereas in general the *trans*-conformation of the peptide bond is highly preferred, *cis*- and *trans*-conformations of Xaa-Pro peptide bonds show comparable thermodynamic stability. This was shown first for short peptides like (*S*-benzyl)-Cys-Pro-Leu-Gly-NH_2 on the basis of

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[7]) TBTU = *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate; HOBt = 1-hydroxybenzotriazole.

[8]) The configurations of (*R*,*S*,*S*)-**8g** and (*R*,*S*)-**8h** were established by X-ray crystallography (see chapter 2.3).

their ^{1}H-NMR spectra [30]. Later, it has been demonstrated that ^{13}C-NMR spectroscopy is a convenient method for distinguishing between the *cis*- and *trans*-conformation of the Xaa-Pro bond [31]. Typically, the chemical shifts of C(*β*)(Pro) and C(*γ*)(Pro) in *cis*-Xaa-Pro peptides are *ca.* 31.3 and 22.5 ppm, respectively, whereas the corresponding values for *trans*-Xaa-Pro peptides are 29.5 and 24.2 ppm [31c]. Obviously, the chemical shift difference, *Δδ*, is a [illegible] with values of *ca.* 8.8 for the *cis*- and 5.3 ppm for the *trans*-conformation. For this reason, we analyzed the ^{13}C-NMR spectra of the prepared Pro-containing pentapeptides **8d**, (*R*,*S*,*S*)- and (*S*,*S*,*S*)-**8g**, (*R*,*S*)- and (*S*,*S*)-**8h**, and **10** (*Table 1*). In all cases, only one conformation was observed with *Δδ* between 2.3 and 2.7 ppm, indicating the *trans*-conformation. This result corresponds with that of the crystal structure determination (chapter 2.3), *i.e.*, the Xaa-Pro peptide bond adopts the same conformation in solution and in the crystal.

Table 1. *^{13}C-NMR Chemical Shifts of C(β) and C(γ) of the Pro Residue in Pro-Containing Pentapeptides*

2.3. *Crystal Structures of Pentapeptides*. – Suitable crystals of the tetrapeptide Z-Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-N(Me)Ph (**6a**) were obtained from CH_2Cl_2/Et_2O/hexane. The crystals are racemic and the asymmetric unit contains one peptide molecule plus one half of a disordered molecule of hexane, which sits across a centre of inversion. In *Fig. 1*, the peptide molecule with the (*S*)-configured amino acid Phe(2Me) is shown. The molecule forms a *β*-turn of type III' [33] with the Phe(2Me) unit in position (i+3) and an intramolecular H-bond N(4)–H$^{\cdots}$O(11) (H$^{\cdots}$O 2.13(3) Å, N$^{\cdots}$O 2.963(3) Å, N–H$^{\cdots}$O 169(3)°). This interaction has a graph set motif [34] of S(10). A second intramolecular H-bond is formed between N(10)–H and N(13). The other two NH groups are involved in intermolecular H-bonds with an adjacent

molecule (N(7)–H···O(2'), N(13)–H···O(5')); these intermolecular interactions link the molecules into extended chains which run parallel to the [010] direction and can be described by graph set motifs of C(8) and C(11), respectively.

Fig. 1. *ORTEP Plot* [32] *of the molecular structure of the tetrapeptide* **6a** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity and only the major conformation of the disordered central benzyl ring is shown, solvent molecule not included)

All peptide bonds show the *trans*-conformation, but the Phe(2Me)-Aib bond deviates significantly from planarity (ω = 155.5(2)°). The values of the torsion angles ω(Gly-Aib), ω(Aib-Phe(2Me)), and ω(Aib-N(Me)Ph) are close to 180° (175.0(2), –176.6(2), and –177.5(2)°). The torsion angles ϕ and ψ of Aib(2) (61.0(4) and 25.3(4)°) and Phe(2Me) (60.2(3) and 23.2(3)°) correspond well with the typical values of +60° and +30° for a left-handed helical structure (β-turn of type III') (*e.g.* [7][35]).

The crystals of the pentapeptide Z-Gly-Aib-(*R*,*S*)-Phe(2Me)-Aib-Gly-OMe (**8a**), obtained from CH_2Cl_2/hexane, are also racemic. The extension of the peptide chain of **6a** by an additional C-terminal Gly-OMe results in the formation of a 3_{10}-helix, *i.e.* three consecutive β-turns of type III/III'. The molecule containing (*S*)-Phe(2Me) again forms a left-handed helix with β-turns of type III' (*Fig. 2*, *Table 2*). Three intramolecular H-bonds stabilize the 3_{10}-helix: N(1)–H···O(8), N(4)–H···O(11), and N(7)–H···O(14) (*Table 3*). All these interactions form formal 10-membered rings (graph set motif S(10)), the last one involving the C=O group of the Z group. The other two NH groups (Gly(1) and Aib(2)) are involved in intermolecular H-bonds with the same O(5')-atom of Phe(2Me) of an adjacent molecule. This O(5')-atom, therefore, accepts two H-bonds, although one of these is quite

weak. The intermolecular H-bonds link the molecules into extended chains which run parallel to the [101] direction and can be described by graph set motifs of C(11) and C(8) for the interactions involving the donors Gly(1) and Aib(2), respectively.

Fig. 2. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **8a** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity)

Table 2. *Torsion Angles* ω, ϕ, and ψ *of the Backbone of the Pentapeptides* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** *in the Crystal* (Amino Acid (*i*) = Gly(1))

Table 3. *Intramolecular H-Bonds of Compounds* **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (atom numbering refers to *Figs. 1 – 7*)

Racemic crystals of Z-Gly-(*R*,*S*)-Phe(2Me)-Gly-Aib-Aib-N(Me)Ph (**8f**) were grown from AcOEt/hexane. In *Fig. 3*, the molecule containing (*S*)-Phe(2Me) is depicted. The asymmetric unit contains one molecule of **8f** and approximately one third of a highly disordered hexane molecule, which sits across a centre of inversion. Four of the five NH groups act as donors for H-bonds. Two of them, N(1)–H and N(4)–H, form intramolecular H-bonds with amide O-atoms that are seven atoms along the peptide backbone to give a graph set motif of S(10) in each case (*Table 3*). These interactions form two β-turns of type III' (*Table 2*), leading to a left-handed helical structure for the molecule containing (*S*)-Phe(2Me). Surprisingly, Gly(3) does not continue this helical structure, and the Z group is turned away from the helix. Rather N(7)–H of Gly(3) forms an intermolecular H-bond with the terminal amide O(24) of a neighboring molecule. The N(13)–H group of Gly(1) forms an

intermolecular H-bond to O(2) of the same neighboring molecule. These intermolecular interactions link the peptide molecules into extended chains, which run parallel to the [010] direction (graph set motifs C(11) and C(14), resp.). Interestingly, N(10)–H is not involved in any H-bonding. Finally, N(1)–H, N(4)–H, N(7)–H, and N(10)–H exhibit the usual weak 'sideways' contacts with one of their neighboring N-atoms. All peptide bonds are in the *trans*-conformation and differ only slightly from planarity, but the terminal amide group deviates significantly from planarity (torsion angle ω –153.1(8)°; *Table 2*).

Fig. 3. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **8f** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecule not included)

The crystals of Z-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OMe ((*S*,*S*)-**8e**) are enantiomerically pure, however the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the *S*-configuration at C(23), resulting from (*S*)-configured H-Phe-OMe used in the synthesis. Based on this, the configuration at C(9) of Phe(2Me) is also *S* (*Fig. 4*). The Ph ring of the terminal benzyl group is disordered over two orientations, with a ratio of the conformers of 0.33:0.67. The crystal lattice also contains one disordered H_2O molecule per peptide molecule. All five peptide NH groups act as donors for H-bonding. Two of the H-bonds are intramolecular interactions with, in each case, the amide O-atom two peptide units further along the peptide chain, forming two consecutive β-turns of type III' (graph set motif: S(10); *Table 3*). As a result of the presence of (*S*)-Phe(2Me), a left-handed helical structure is formed (see *e.g.*, [36]). The presence of (*S*)-Phe, an amino acid which usually forms right-handed helices, probably has no influence because of its position at the C-terminus of the peptide. As in **8f**, the helix is not continued by

Gly(3), and the Z group is turned away. The NH group of Gly(3) forms an intermolecular H-bond with O(2') of Aib(4) of an adjacent molecule. A second intermolecular H-bond, N(13)–H···O(5'), is formed with the same neighboring molecule. These two interactions link the peptide molecules into extended chains, which run parallel to the [100] direction (graph set motifs C(8) and C(11), resp.). The fifth interaction, from N(10)–H of Phe(2Me), involves a H_2O molecule acting as an acceptor. Furthermore, analogous to **8f**, N(1)–H, N(4)–H, N(7)–H, and N(10)–H are close enough to adjacent N-atoms in the peptide chain to form weak interactions.

Fig. 4. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* (*S*,*S*)-**8e** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity and only the major conformation of the disordered terminal benzyl group is shown, water molecules not included)

The asymmetric unit of Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OMe ((*R*,*S*,*S*)-**8g**) contains one peptide molecule, one molecule of AcOEt, and one site for a H_2O molecule, which is partially occupied (50%). The crystals are enantiomerically pure, however the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the known *S* configuration at C(6) and C(23) of the Pro and Phe residues, respectively. Based on this assumption, C(9) of Phe(2Me) has the *R* configuration. The molecule forms a right-handed 3_{10}-helix, as expected for a peptide containing two protein amino acids and (*R*)-Phe(2Me) (*Fig. 1*, *Table 2*). Again, the Z-group is turned away from the helix, in this case because of the presence of Pro in position 3 of the peptide. The N(1)–H and N(4)–H groups of Phe(5) and Aib(4), respectively, from intramolecular H-bonds with amide O-atoms that are seven atoms along the peptide backbone (graph set motif S(10) for each

interaction, *Table 3*). The NH groups of Phe(2Me)(2) and Gly(1), N(10)–H and N(13)–H, respectively, form intermolecular H-bonds with the amide O-atoms, O(5') and O(2"), respectively, of different neighboring molecules. The N(10)–H interaction links the molecules into extended chains, which run parallel to the [100] direction (graph set motif C(8)), while the N(13)–H interaction links the molecules into a second type of extended chains, which also run parallel to the [100] direction (graph set motif C(14)). The H_2O molecule acts as a donor for two H-bonds to amide O-atoms of two different peptide molecules (graph set motif D for each interaction). As a result, the amide O-atoms O(2) of Aib(4) and O(11) of Gly(1) are each acceptors of two H-bonds. Neither the H_2O molecule nor the AcOEt molecule acts as an acceptor for H-bonds. The combination of all intermolecular interactions links the molecules into extended sheets, which lie parallel to the (010) plane. Finally, N(1)–H and N(4)–H exhibit the usual weak 'sideways' contacts with one of their neighboring N-atoms.

Fig. 5. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* (*R*,*S*,*S*)-**8g** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecules not included)

The crystals of Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph (□*R*□*S*□-**8h**) are enantiomerically pure, however the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the known *S* configuration of the Pro residue (C(6)). The configuration of Phe(2Me), at (C(9)), is therefore *R* (*Fig. 6*). The asymmetric unit contains two independent peptide molecules, one hexane molecule, and a H_2O molecule, which lies on a twofold axis. The two peptide molecules have generally similar conformations with the major difference being in the orientation of the Ph rings at each end of the peptide chain. One of the peptide molecules (molecule B) has disorder in the

Ph ring of the protecting group Z. In molecule A, the NH groups of the two Aib units, N(1)–H and N(4)–H, form intramolecular H-bonds with O(8) of Phe(2Me) and O(11) of Gly, respectively, resulting in two *β*-turns of type III (graph set motifs of S(10), *Table 3*). The same interactions occur in molecule B, involving N(51)–H and N(54)–H. These are the normal intramolecular interactions found for peptides of this type and help to form a right-handed 3_{10}-helical structure (*Table 2*). These NH groups also have weak 'sideways' interactions with the next neighboring N-atom in the chain. The other NH groups and the H_2O molecule act as donors for intermolecular H-bonds: N(10)–H in molecule A forms an H-bond with the amide O-atom, O(74), at the opposite end of molecule B. The corresponding group, N(60)–H, in molecule B, however, interacts with a different O-atom in another molecule A, namely O(2). These two interactions form spiralling ····A····B····A····B···· chains of molecules which run parallel to the [001] direction and have a binary graph set motif of $C^2_2(25)$. Furthermore, N(13)–H of molecule A forms an intermolecular H-bond with the amide O-atom of Pro(3), O(55), of molecule B and the same interaction, involving N(63)–H, occurs to link molecule B to atom O(5) of a different molecule A, thus forming extended ····A····B····A····B···· chains of molecules, which run parallel to the [010] direction (graph set motif $C^2_2(22)$). The H_2O molecule sits on a two-fold axis and therefore acts as a donor for two equivalent H-bonds to the amide O-atom O(52) of Aib(4) in two different B molecules (graph set motif D). The combination of the intermolecular interactions links the molecules into three-dimensional supramolecular frameworks.

Fig. 6. *ORTEP Plot* [32] *of the molecular structure of one of the two symmetry-independent molecules of the pentapeptide* (*R*,*S*)-**8h** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecules not included)

The crystals of Z-Gly-Aib-Pro-Aib-Aib-OH (**10**) are enantiomerically pure, however the absolute configuration has not been determined. The enantiomer used in the refinement was based on the known *S* configuration of Pro (C(6)). The asymmetric unit contains one peptide and one disordered MeOH molecule. Two intramolecular H-bonds, N(1)–H···O(8) and N(4)–H···O(11), form two β-turns of type III (graph set motif S(10), *Table 3*), *i.e.*, a right-handed 3_{10}-helix, as expected for a peptide containing (*S*)-Pro as the only chiral amino acid. The other two NH groups, N(10)–H and N(13)–H, as well as the carboxyl OH group, O(25)–H, form intermolecular H-bonds with carbonyl O-atoms in three different neighboring molecules. The O(25)–H···O(5') interaction links the molecules into extended chains which run parallel to the [100] direction and have a graph set motif C(10)). The N(10)–H···O(2") interaction links the molecules into extended chains which run parallel to the [010] direction (graph set motif C(11)), while the N(13)–H···O(8''') interaction links the molecules into extended chains which also run parallel to the [100] direction (graph set motif C(8)). The combination of these intermolecular interactions links the molecules into a two-dimensional network, which lies parallel to the (001) plane. The O(8)-atom acts as an acceptor for two H-bonds, an intra- and an intermolecular one. Both positions for the disordered MeOH molecule indicate the presence of a H-bond to the carbonyl O(14)-atom.

Fig. 7. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **10** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecule not included)

3. Conclusions. – The present results prove once more the usefulness of the 'azirine/oxazolone method', combined with traditional segment coupling, in the synthesis of

peptides containing α,α-disubstituted α-amino acids. All of the Aib and Phe(2Me) residues, as well as the 1-aminocyclobutane carboxylic acid, have been added to *N*-protected amino acids or peptides *via* the reaction with the corresponding 2,2-disubstituted 2*H*-azirin-3-amine **1**. As shown in previous studies [7][8][25][37], the coupling of two α,α-disubstituted α-amino acids does not suffer from steric hindrance. This is of importance because coupling reactions with *N*-terminal Aib residues are known to be difficult (see *e.g.* [38]). As the synthon for Phe(2Me), **1b**, was used as a racemate[2]), racemic pentapeptides such as **8a** or mixtures of epimers such as **8b** were formed. The pure epimers were obtained after chromatographic separation in the cases of **8e**, **8g**, and **8h**.

It is also important to note that the segment coupling with dipeptides with a *C*-terminal Aib or Phe(2Me) residue could be performed in good yields, even in the case of tripeptides **9** and **13** with a *N*-terminal Pro. Surprisingly, the coupling with TBTU/HOBt yielded the pentapeptides **8g** and **8h** in significantly higher yield than with PyBOP, which was the preferred coupling reagent in the cases without Pro.

The X-ray crystal-structure determinations showed that all of the prepared pentapeptides adopt a 3_{10}-helical conformation, as expected for Aib-containing peptides [39]. As Aib is achiral, the handedness of the helix is determined by the chiral amino acid present. It has been shown that a right-handed helix is preferred when the poly-Aib peptide contains a *N*-terminal L-amino acid or a L-amino acid within the peptide chain [40]. On the other hand, a *C*-terminal L-amino acid leads to the inverse relationship, *i.e.*, a left-handed helix. Furthermore, it was found that the chiral α,α-disubstituted α-amino acid Phe(2Me) has the opposite effect, *i.e.*, an internal L-Phe(2Me) residue induces a left-handed helix [36a][41]. Recently, a similar reversal of the screw-sense induction was described for the amino acids Val and Val(2Me): the hexapeptides Ac-L-Xaa-$(Aib)_4$-Gly NH_2 and pentapeptides Ac-L-Xaa-$(Aib)_4$-OR form left-handed helices with Xaa = Val but right-handed helices with Xaa =

Val(2Me) [42]. The study of the influence of the type and the position of L- and D-amino acids on the helical screw sense of Aib-containing peptides is a topic of current interest (see, *e.g.*, [43]).

The crystal structures of the prepared pentapeptides are in full accordance with the results reported in [36][41]. Whereas the peptide **10** with (*S*)-Pro as the only chiral amino acid adopts a right-handed 3_{10}-helical structure, as is 'normal' for protein amino acids, the enantiomers of the racemic peptides **8a** and **8f**, containing (*S*)-Phe(2Me) in position 3 and 2, respectively, exist in a left-handed 3_{10}-helical conformation in the crystal. Furthermore, in the crystal of the racemic tetrapeptide **6a**, the enantiomer with (*S*)-Phe(2Me) forms a β-turn of type III', *i.e.*, a turn with a left-handed helical structure. On the other hand, both (*R*,*S*,*S*)-**8g** and (*R*,*S*)-**8h** form right-handed 3_{10}-helices, supported by the presence of (*R*)-Phe(2Me) as well as (*S*)-Pro in position 3.

It is worth mentioning that in **8a** three intramolecular (1←4) H-bonds are formed, stabilizing the 3_{10} helix (*Table 3*). One of them is the interaction of N(7)–H of Phe(2Me) with C=O(14) of the Z protecting group. Surprisingly, only two intramolecular (1←4) H-bonds are present in the analogous pentapeptide **8f**, and the Z group is not involved in an intramolecular H-bond. The analogous H-bond pattern with only two (1←4) interactions, is observed in the enantiomerically pure (*S*,*S*)-**8e**. In both cases, N(7)–H of Gly(3) does not form intramolecular H-bonds. In the two remaining pentapeptides (*R*,*S*,*S*)-**8g** and (*R*,*S*)-**8h**, which possess a Pro(3) unit, only two intramolecular (1←4) H-bonds, N(1)–H$^{\cdots}$O(8) and N(4)–H$^{\cdots}$O(11), are possible.

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Experimental part

1. *Abbreviations*. Acb, 1-aminocyclobutane carboxylic acid; Aib, 2-aminoisobutyric acid (2-methylalanin); CSA, camphor-10-sulfonic acid; DCC, *N*,*N'*-dicyclohexylcarbodiimide; DEPC, diethyl cyanophosphonate; DIEA, ethyl(diisopropyl)amine (*Hünig* base); DPPA, diphenyl phosphorazidate; HBPyU, *O*-[(benzotriazol-1-yl)oxy]dipyrrolidinocarbenium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; PyBOP = [(benzotriazol-1-yl)oxy]tripyrrolidinophosphonium hexafluorophosphate; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; Z, benzyloxycarbonyl.

2. *General.* See [11][25]. Amino acids were purchased from *Novabiochem* and *Bachem* and are all L-configured, other reagents and solvents from *Aldrich*, *Bachem, Fluka* and *Merck*, resp. Solvents were purified by standard procedures. TLC: *Merck* TLC glass plates, silica gel *60* F_{254}. Preparative layer chromatography (PLC): *Merck* glass plates, silica gel *60* F_{254}. Column chromatography (CC): *Uetikon-Chemie*, silica gel *C-560* (0.04-0.063 mm). M.p. were measured on a *Mettler-FP-5* apparatus, uncorrected. $[\alpha]_D$-Values were determined on a *Perkin-Elmer-241* polarimeter at 21°. IR Spectra were recorded on a *Perkin-Elmer-781* spectrometer, in KBr. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a *Bruker AC-300* or *Bruker ARX-300* spectrometer at 300 (^{1}H) and 75.5 MHz (^{13}C), respectively, in $CDCl_3$, CD_3OD or (D_6)DMSO. The multiplicity of ^{13}C signals was determined by the DEPT technique. ESI-MS were measured on a *Finnigan TSQ-700* instrument, and CI-MS (with NH_3 or isobutane) on a *Finnigan MAT-90* or *SSQ-700* instrument; *m/z* (rel. %).

*General Procedure 1 (GP 1, Coupling with 2*H*-Azirin-3-amines).* To a soln. of an N-protected amino acid or N-protected peptide (1 mmol) in abs. THF (5 ml) at 0°, 1.1 equiv. of the corresponding 2*H*-azirin-3-amine in THF were added, and the mixture was stirred at r.t.

for several h (Ar atmosphere). After completion of the reaction, the solvent was evaporated and the product was purified by crystallization from CH_2Cl_2/hexane or AcOEt/hexane. In the case of incomplete reactions, the residue was dissolved in CH_2Cl_2, the remaining acid extracted with 1N aq. NaOH, the solvent evaporated, and the residue crystallized.

General Procedure 2 (GP 2, Selective Hydrolysis of Peptide N-*Methyl*-N-*phenylamides).* A soln. of the peptide amide (1 mmol) in 3N HCl (THF/H_2O (1:1); 10 ml) was stirred at r.t. for 1–60 h. Then, aq. 2N HCl was added, and the mixture was extracted with Et_2O. The org. layers were combined, dried (Na_2SO_4), and the solvent evaporated.

General Procedure 3 (GP 3, Hydrogenolytic Deprotection). The Z-protected peptide (1 mmol) was dissolved in MeOH, and 10 weight% Pd/C (10%) was added to the soln. The mixture was stirred at r.t. under an H_2 atmosphere overnight. Then, the soln. was filtered through a pad of *Celite* and the solvent was evaporated. The product was dried in high vacuum (*i.v.*).

General Procedure 4 (GP 4, Deprotection via *Catalytic Hydrogen Transfer* [44]*).* To a soln. of Z-protected peptide (1 mmol) in MeOH were added 10 weight% Pd/C (10%) and HCO_2NH_4 (5 mmol). The mixture was heated at reflux (10 min) and filtered through a pad of *Celite*, washed with MeOH, and the solvent was evaporated.

General Procedure 5 (GP 5, Coupling of Amino Acids). To a soln. of a Z-protected peptide (1 mmol), an amino acid ester (1.1 mmol), and a coupling reagent (1 mmol) in CH_2Cl_2 (1 ml) was added drop-wise DIEA (2 mmol; 3 mmol by using the hydrochloride of the amino acid ester) at r.t. The soln. was stirred for 1 h, and then the solvent evaporated. The residue was dissolved in AcOEt (20 ml), washed with 5% aq. $KHSO_4$ (3×), 5% aq. $NaHCO_3$ (3×), and sat. aq. NaCl soln., and purified by CC.

3. *Synthesis of the Pentapeptides* **8**. 3.1. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OMe* (**8a**). 3.1.1. *Z-Gly-Aib-(*R,*S)-Phe(2Me)-N(Me)Ph* (**4a**). According to *GP 1*, to a soln. of Z-Gly-

Aib-OH (**3**) [25] (4.49 g, 15.3 mmol) in abs. THF (70 ml) at 0° was added 2-benzyl-2,*N*-dimethyl-*N*-phenyl-2H-azirin-3-amine (**1b**; 15.1 g of a *ca.* 3:4 mixture of **1b** and 2-benzyl-*N*-methyl-*N*-phenylpropanamide (*ca*. 25.9 mmol **1b**)); stirring at r.t. for 70 h. The solvent was evaporated and the product purified by CC (CH_2Cl_2/MeOH 97:3): 5.95 g (72%) of **4a**. Colorless foam. M.p. 72.2–73.1°. IR (KBr): 3320*m*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1640*s*, 1590*s*, 1515*s*, 1495*s*, 1450*s*, 1380*m*, 1365*m*, 1260*m*, 1240*m*, 1190*m*, 1155*m*, 1105*m*, 1080*m*, 1050*m*, 770*m*, 735*m*, 700*s*. ^{1}H-NMR ($CDCl_3$): 7.46 (*s*, NH); 7.4–7.2 (*m*, 11 arom. H); 7.15–7.05 (*m*, 4 arom. H); 6.85 (*s*, NH); 5.62 (br. *s*, NH); 5.11 (*s*, PhC*H*$_2$O); 3.77 (*d*, *J* = 5.4, CH_2(Gly)); 3.48, 3.06 (*AB*, J_{AB} = 14.2, PhC*H*$_2$); 3.31 (*s*, MeN); 1.42 (*s*, Me_2C); 1.33 (*s*, Me(Phe(2Me)). ^{13}C-NMR ($CDCl_3$): 172.6, 172.5, 168.1 (3*s*, 3 CO(amide)); 156.5 (*s*, CO(urethane)); 144.1, 136.4, 136.3 (3*s*, 3 arom. C); 129.8, 129.5, 128.5, 128.2, 128.1, 128.0, 127.0 (7*d*, 15 arom. CH); 67.0 (*t*, $PhCH_2O$); 63.2, 57.5 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 44.9 (*t*, CH_2(Gly)); 42.3 (*t*, $PhCH_2$); 41.8 (*q*, MeN); 24.9, 24.6, 23.5 (3*q*, *Me*$_2$C, Me(Ph(2Me))). CI-MS: 545 (7, $[M+1]^+$), 439 (13), 438 (53, $[M–Ph(Me)N]^+$), 437 (100, $[M–PhCH_2O]^+$), 412 (8), 411 (15). Anal. calc. for $C_{31}H_{36}N_4O_5$ (544.65): C 68.36, H 6.66, N 10.29; found: C 67.96, H 6.90, N 10.35.

3.1.2. *Z-Gly-Aib-(*R,*S)-Phe(2Me)-OH* (**5a**). According to *GP 2*, a soln. of **4a** (5.86 g, 10.8 mmol) in 3N HCl was stirred at r.t. for 7 h. The solvent was evaporated and the precipitate was filtered: 4.50 g (92%) of **5a**. Colorless crystals. M.p. 192.6–193.8°. IR (KBr): 3310*m*, 3040*m*, 2980*m*, 2970*m*, 1720*s*, 1660*s*, 1650*s*, 1560*m*, 1525*s*, 1460*m*, 1450*m*, 1440*m*, 1285*m*, 1275*m*, 1245*s*, 1195*m*, 1165*m*, 1130*m*, 700*m*. ^{1}H-NMR ((D_6)DMSO): 12.6 (br. *s*, COOH); 7.96 (*s*, NH); 7.49 (*t*, *J* = 5.8, NH(Gly)); 7.35–7.15 (*m*, 8 arom. H, NH); 7.1–7.05 (*m*, 2 arom. H); 5.00 (*s*, PhC*H*$_2$O); 3.58 (*d*, *J* = 6.0, CH_2(Gly)); 3.17 (*s*, PhC*H*$_2$); 1.39, 1.35, 1.30 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ((D_6)DMSO): 175.2, 173.5, 169.0 (3*s*, 2 CO (amide), COOH); 156.8 (*s*, CO(urethane)); 137.4, 137.0 (2*s*, 2 arom. C); 130.7, 128.7, 128.1, 128.0,

126.8 (5*d*, 10 arom. CH); 65.8 (*t*, Ph*C*H_2O); 59.5, 56.6 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 44.2 (*t*, CH_2(Gly)); 41.0 (*t*, Ph*C*H_2); 25.4, 24.8, 22.7 (3*q*, *Me*$_2$C, Me(Phe(2Me))). CI-MS: 457 (6), 456 (24, $[M+1]^+$), 439 (28), 438 (100, $[M–H_2O+1]^+$), 348 (12), 330 (8), 312 (12), 295 (47), 277 (15, $[M–$Phe(2Me)$]^+$, 251 (18), 180 (30), 134 (26). Anal. calc. for $C_{24}H_{29}N_3O_6$ (455.51): C 63.28, H 6.42, N 9.22; found: C 62.99, H 6.31, N 9.05.

3.1.3. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-N(Me)Ph* (**6a**). According to *GP 1*, **5a** (931 mg, 2.04 mmol) was reacted with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a** [26]; 395 mg, 2.27 mmol) in THF/DMF (20:1; 21 ml) for *ca.* 70 h: 1.21 g (94%) of **6a**. Colorless crystals. M.p. 91.3–93.0°. IR (KBr): 3420*m*, 3320*m*, 3280*m*, 1720*s*, 1680*s*, 1650*s*, 1635*s*, 1590*m*, 1530*s*, 1495*s*, 1455*m*, 1395*m*, 1380*m*, 1365*m*, 1280*m*, 1240*s*, 1215*m*,1195*m*, 1170*m*, 1100*m*, 1090*m*, 1050m, 740*m*, 705*s*. ^{1}H-NMR ($CDCl_3$): 7.66 (*s*, NH); 7.35–7.15 (*m*, 13 arom. H); 7.1–7.05 (*m*, 2 arom. H); 6.87, 6.56, 6.18 (3*s*, 3 NH); 5.03, 4.98 (*AB*, J_{AB} = 12.2, PhC*H*$_2$O); 3.65–3.55 (*m*, CH_2(Gly), 1H of PhC*H*$_2$); 3.35 (*s*, MeN); 3.09 (*d*, J_{AB} = 13.7, 1H of PhC*H*$_2$); 1.46 (*s*, Me_2C); 1.42, 1.38, 1.27 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 174.0, 173.5, 172.9, 170.3 (4*s*, 4 CO(amide)); 157.1 (*s*, CO(urethane)); 145.6, 136.8, 136.2 (3*s*, 3 arom. C); 130.9, 129.2, 128.5, 128.2, 128.0, 127.9, 127.5, 127.0, 126.7 (9*d*, 15 arom. CH); 67.0 (*t*, Ph*C*H_2O); 60.2, 57.6, 57.2 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 45.3 (*t*, CH_2(Gly)); 40.5 (*q*, MeN); 40.3 (*t*, Ph*C*H_2); 25.8, 25.5, 24.3 (3*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 668 (29, $[M+K]^+$, 652 (100, $[M+Na]^+$, 523 (47, $[M–$N(Me)Ph$]^+$). Anal. calc. for $C_{35}H_{43}N_5O_6$ (629.76): C 66.75, H 6.88, N 11.12; found: C 66.55, H 6.67, N 11.00.

Suitable crystals for the X-ray crystal-structure determination were grown from CH_2Cl_2/Et_2O/hexane by slow evaporation of the solvent.

3.1.4. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-OH* (**7a**). According to *GP 2*, **6a** (4.12 g, 6.55 mmol) was hydrolyzed for 3.5 h: 3.21 g (91%) of **7a**. Colorless solid. M.p. 193.5–195.7°. IR (KBr): 3400*m*, 3300*m*, 2980*m*, 1760*s*, 1680*s*, 1650*s*, 1530*s*, 1500*m*, 1470*m*, 1455*m*, 1390*m*,

1315*m*, 1280*m*, 1240*m*, 1160*m*, 700*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.27 (*s*, NH); 7.51 (*t*, *J* = 5.5, NH(Gly)); 7.47 (*s*, NH); 7.4–7.2 (*m*, 8 arom. H); 7.15–7.1 (*m*, 2 arom. H); 6.97 (*s*, NH); 5.01, 4.98 (*AB*, J_{AB} = 13.4, PhC*H*$_2$O); 3.7–3.5 (*ABX*, J_{AB} = 16.3, CH$_2$(Gly)); 3.40, 2.99 (*AB*, J_{AB} = 13.4, PhC*H*$_2$); 1.36, 1.35, 1.33, 1.30, 1.22 (5*s*, 2 Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (CDCl$_3$): 175.5, 172.82, 172.78, 169.9 (4*s*, 3 CO(amide), COOH); 156.6 (*s*, CO(urethane)); 137.0, 136.7 (2*s*, 2 arom. C); 130.7, 128.2, 127.73, 127.68, 127.5, 126.1 (6*d*, 10 arom. CH); 65.6 (*t*, Ph*C*H$_2$O); 58.7, 56.1, 54.7 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 43.6 (*t*, CH$_2$(Gly)); 39.2 (*t*, Ph*C*H$_2$); 25.6, 24.9, 24.3, 24.2, 23.2 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 563 (100, [*M*+Na]$^+$). Anal. calc. for C$_{28}$H$_{36}$N$_4$O$_7$ (540.62): C 62.21, H 6.71, N 10.36; found: C 62.15, H 6.70, N 10.34.

3.1.5. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Gly-OMe* (**8a**). According to *GP 5*, **7a** (2.46 g, 4.54 mmol) was coupled with H-Gly-OMe.HCl (639 mg, 5.09 mmol) by treatment with PyBOP (2.22 g, 4.63 mmol) and DIEA (1.81 g, 13.97 mmol) in CH$_2$Cl$_2$ (7 ml); 1 h. CC with AcOEt gave 2.54 g (91%) **8a**. Colorless foam. M.p. 160.3–161.3°. IR (KBr): 3340*m*, 3320*s*, 3000*s*, 2960*m*, 1755*s*, 1705*s*, 1675*s*, 1650*s*, 1530*s*, 1460*m*, 1385*m*, 1365*m*, 1305*m*, 1290*m*, 1260*m*, 1240*m*, 1215*m*, 1195*m*, 1180*m*, 1160*m*, 975*m*, 740*m*, 710*m*, 700*m*. ^{1}H-NMR (CDCl$_3$): 7.81 (*t*, NH(Gly)); 7.41 (*s*, NH); 7.35–7.2 (*m*, 8 arom. H); 7.1–7.05 (*m*, 2 arom. H); 6.90, 6.82 (2*s*, 2 NH); 6.08 (*t*-like, NH(Gly)); 4.97 (*s*, PhC*H*$_2$O); 3.95 (*d*, *J* = 5.9, CH$_2$(Gly)); 3.71–3.70 (*m*, CH$_2$(Gly)); 3.56 (*s*, MeO); 3.23, 3.03 (*AB*, J_{AB} = 13.7, PhC*H*$_2$); 1.49, 1.46, 1.39, 1.37 (4*s*, 2 Me$_2$C, Me(Phe(2Me))). ^{13}C-NMR (CDCl$_3$): 176.2, 174.8, 173.8, 171.5, 170.5 (5*s*, 4 CO(amide), COOMe); 157.3 (*s*, CO(urethane)); 136.1, 136.0 (2*s*, 2 arom. C); 130.8, 128.6, 128.3, 128.1, 127.9, 127.0 (6*d*, 10 arom. CH); 67.1 (*t*, Ph*C*H$_2$O); 59.9, 57.3, 57.0 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 52.2 (*s*, MeO); 45.4, 41.4, 41.1 (3*t*, 2 CH$_2$(Gly), Ph*C*H$_2$); 26.2, 25.4, 24.5, 23.4 (4*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 650 (5, [*M*+K]$^+$), 634 (100,

[*M*+Na]$^+$], 612 (3, [*M*+1]$^+$). Anal. calc. for $C_{31}H_{41}N_5O_8$ (611.69): C 60.87, H 6.76, N 11.45; found: C 60.78, H 6.63, N 11.44.

Suitable crystals for the X-ray crystal-structure determination were grown from CH_2Cl_2/hexane by slow evaporation of the solvent.

3.2. *Z-Gly-Aib-(*R,S*)-Phe(2Me)-Aib-Phe-OBn* (**8b**). According to *GP 5*, **7a** (432 mg, 0.779 mmol) was coupled with H-Phe-OBn.HCl (250 mg, 0.857 mmol) by treatment with PyBOP (373 mg, 0.779 mmol) and DIEA (307 mg, 2.205 mmol) in CH_2Cl_2 (3 ml); 5.5 h. CC with AcOEt/hexane 3:1 gave 527 mg (85%) **8b** (mixture of diastereoisomers). Colorless solid. M.p. 134.0–136.5°. $[\alpha]_D$ = –20.3 (c = 0.5, EtOH). IR (KBr): 3300*m*, 1740*m*, 1700*m*, 1660*s*, 1535*s*, 1500*m*, 1455*m*, 1275*m*, 1240*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.78 (*m*, NH); 7.46, 7.36 (2*s*, 1 NH); 7.25–7.15 (*m*, 18 arom. H); 7.1–7.05 (*m*, 2 arom. H); 6.69, 6.93 (2*s*, 1 NH); 6.75, 6.71 (2*s*, 1 NH); 6.22, 6.17 (2 br. *s*, 1 NH); 5.01 (*s*, PhC*H*$_2$O); 5.0–4.9 (*m*, PhC*H*$_2$O); 4.75–4.65 (*m*, CH(Phe)); 3.65–3.6 (*m*, CH_2(Gly)); 3.37, 3.2–3.1, 3.02 (*t*,*m*,*d*, *J* = 15.6, 13.7, 1:2:1, 2 PhC*H*$_2$); 1.46, 1.44, 1.40, 1.37, 1.34, 1.33 (6*s*, 2 Me_2C; Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.7, 174.1, 173.0, 172.1, 170.3 (5*s*, 4 CO(amide), COOBn); 157.3 (*s*, CO(urethane)); 137.1, 136.1, 135.5 (3*s*, 3 arom. C); 130.9, 129.3, 129.2, 128.5, 128.4, 128.3, 128.12, 128.09, 128.0, 126.9, 126.6 (11*d*, 20 arom. CH); 67.1, 66.8, 66.7 (3*t*, 2 Ph*C*H$_2$O); 59.9, 57.0 (2*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 54.5 (*d*, CH(2)Phe); 45.4, 37.5 (2*t*, CH_2(Gly), 2 Ph*C*H$_2$); 25.7, 25.0, 24.5, 24.1, 23.4 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 801 (100, [*M*+Na]$^+$). Anal. calc. for $C_{44}H_{51}N_5O_8$ (777.92): C 67.94, H 6.61, N 9.00; found: C 67.79, H 6.88, N 9.00.

3.3. *Z-Gly-Aib-Acb-Aib-Gly-OMe* (**8c**). 3.3.1. *Z-Gly-Aib-Acb-NMe*$_2$ (**4b**). According to *GP 1*, **3** (1.68 g, 5.72 mmol) was reacted with 2-dimethylamino-1-azabicyclo[2.3]hex-1-ene (**1c**) [2b] (782 mg, 6.30 mmol) in THF (16 ml); *ca.* 1 h. The precipitate was filtered and washed with Et_2O: 1.02 g of **8c**. CC (CH_2Cl_2/MeOH 10:1) of the filtrate gave another 1.06 g of **8c**. Total yield: 2.08 g (87%). Colorless solid. M.p. 212.3–213.7°. IR (KBr): 3340*m*, 3270s,

3050*m*, 2980*m*, 2940*m*, 1730*s*, 1710*m*, 1680*m*, 1660s, 1630*s*, 1540*m*, 1530*m*, 1395*m*, 1270*m*, 1245*m*, 1230*m*, 750*w*, 700*w*. ^{1}H-NMR ((D$_6$)DMSO): 7.90, 7.89 (2*s*, 2 NH); 7.56 (*t*-like, NH); 7.35–7.3 (*m*, 5 arom. H); 5.05 (*s*, PhC*H*$_2$O); 3.61 (*d*, *J* = 5.8, CH$_2$(Gly)); 3.33 (*s*, Me$_2$N); 2.6–2.5, 2.2–2.1, 1.76–1.74, 1.6–1.55 (4*m*, 2:2:1:1, 3 CH$_2$(Acb)); 1.36 (*s*, Me$_2$C). ^{13}C-NMR ((D$_6$)DMSO): 175.2, 170.6, 168.4 (3*s*, 3 CO(amide)); 156.6 (*s*, CO(urethane)); 136.9 (*s*, 1 arom. C); 128.3, 127.7, 127.5 (3*d*, 5 arom. CH); 65.4 (*t*, Ph*C*H$_2$O); 58.2, 55.7 (2*s*, C(2)(Aib), C(2)(Acb)); 44.0 (*t*, CH$_2$(Gly)); 36.8, 36.0 (2*q*, Me$_2$N); 30.9 (*t*, 2 CH$_2$(Acb)); 24.8 (*q*, *Me*$_2$C), 14.3 (*t*, CH$_2$(Acb)). ESI-MS: 441 (100, [*M*+Na]$^+$).

3.3.2. *Z-Gly-Aib-Acb-OH* (**5b**). According to *GP 2*, **4b** (372 mg, 0.890 mmol) was hydrolyzed for 70 h at 40°: 334 mg (96%) of **5b**. Colorless crystals. M.p. 180.5–182.3°. IR (KBr): 3340*s*, 3290s, 3060*m*, 2980*m*, 2950*m*, 1720*s*, 1680*s*, 1670s, 1650*s*, 1565*m*, 1550*s*, 1540*s*, 1525*m*, 1470*m*, 1430*s*, 1385*m*, 1280*s*, 1250*s*, 1235*m*, 1165*m*, 1110*m*, 750*m*. ^{1}H-NMR (CD$_3$OD): 7.4–7.25 (*m*, 5 arom. H); 5.11 (*s*, PhC*H*$_2$O); 3.72 (*s*, CH$_2$(Gly)); 2.65–2.5, 2.4–2.3, 2.05–1.85 (3*m*, 3 CH$_2$(Acb)); 1.44 (*s*, Me$_2$C). ^{13}C-NMR (CD$_3$OD): 175.5, 174.8, 170.1 (3*s*, 2 CO(amide), COOH); 157.8 (*s*, CO(urethane)); 136.6 (*s*, 1 arom. C); 128.0, 127.5, 127.3 (3*d*, 5 arom. CH); 66.3 (*t*, Ph*C*H$_2$O); 58.2, 56.2 (2*s*, C(2)(Aib), C(2)(Acb)); 44.0 (*t*, CH$_2$(Gly)); 30.5 (*t*, 2 CH$_2$(Acb)); 23.8 (*q*, *Me*$_2$C), 14.8 (*t*, CH$_2$(Acb)). ESI-MS: 430 (51, [*M*+K]$^+$), 414 (100, [*M*+Na]$^+$). Anal. calc. for C$_{19}$H$_{25}$N$_3$O$_6$·0.5H$_2$O (400.43): C 56.99, H 6.54, N 10.49; found: C 57.25, H 6.77, N 10.76.

3.3.3. *Z-Gly-Aib-Acb-Aib-N(Me)Ph* (**6b**). According to *GP 1*, **5b** (840 mg, 2.15 mmol) was reacted with **1a** (411 mg, 2.36 mmol) in THF/DMF (29 ml, 28:1). CC (CH$_2$Cl$_2$/MeOH 10:1) gave 1.14 g (94%) of **6b**. Colorless solid. Phase transitions at 137 and 167°; m.p. 187.8–188.3°. IR (KBr): 3300*s*, 3060*m*, 2990*m*, 2940*m*, 1710*s*, 1680*s*, 1675*s*, 1670*s*, 1660s, 1650*s*, 1645*s*, 1630*s*, 1605*m*, 1590*m*, 1550*s*, 1540*s*, 1530*s*, 1520*s*, 1505*s*, 1495*s*, 1470*s*, 1395*m*, 1275*m*, 1265*m*, 1240*s*, 1190*m*, 1155*m*, 1090*m*, 700*m*. ^{1}H-NMR (CD$_3$OD): 7.51 (br. *s*, 2 NH);

7.4–7.2 (*m*, 10 arom. H); 6.58 (br. *s*, NH); 6.44 (*s*, NH); 5.15 (*s*, PhC*H*$_2$O); 3.70 (*d*, *J* = 5.2, CH$_2$(Gly)); 3.30 (*s*, MeN); 2.7–2.55, 2.15–1.95, 1.95–1.8 (3*m*, 2:3:1, 3 CH$_2$(Acb)); 1.44, 1.28 (2*s*, 2 Me$_2$C). ^{13}C-NMR (CDCl$_3$): 174.0, 173.7, 173.5, 170.7 (4*s*, 4 CO(amide)); 157.6 (*s*, CO(urethane)); 146.0, 136.5 (2*s*, 2 arom. C); 129.2, 128.5, 128.2, 127.8, 127.3, 127.0 (6*d*, 10 arom. CH); 67.0 (*t*, Ph*C*H$_2$O); 59.2, 56.8, 56.6 (3*s*, 2 C(2)(Aib), C(2)(Acb)); 45.7 (*t*, CH$_2$(Gly)); 40.5 (*q*, MeN); 31.6, 31.3 (2*t*, 2 CH$_2$(Acb)); 25.7, 24.9 (2*q*, 2 *Me*$_2$C), 16.0 (*t*, CH$_2$(Acb)). ESI-MS: 588 (100, [*M*+Na]$^+$), 459 (5, [*M*– N(Me)Ph]$^+$), 374 (26, [*M*–Aib-N(Me)Ph]$^+$), 277 (3, [*M*–Acb-Aib-N(Me)Ph)]$^+$).

3.3.4. *Z-Gly-Aib-Acb-Aib-OH* (**7b**). According to *GP 2*, **6b** (1.033 g, 1.83 mmol) was hydrolyzed and the product extracted with AcOEt: 828 mg (95%) of **7b**. Colorless solid. M.p. 201.4–203.6°. IR (KBr): 3350*m*, 3320*s*, 3270*s*, 3000*m*, 2960*m*, 1730*s*, 1705*s*, 1670*s*, 1660*s*, 1650*s*, 1635*s*, 1605*m*, 1545*s*, 1540*s*, 1530*s*, 1470*m*, 1465*m*, 1395*m*, 1330*m*, 1310*m*, 1290*m*, 1260*s*, 1245*s*, 1215*m*, 1170*m*, 1150*m*, 970*m*, 745*m*. ^{1}H-NMR (CD$_3$OD): 8.40 (*s,* 0.3 NH); 7.98 (*s*, NH); 7.34 (*s*, 0.7 NH); 7.4–7.25 (*m*, 10 arom. H); 5.08 (*s*, PhC*H*$_2$O); 3.71 (*s*, CH$_2$(Gly)); 2.7–2.6, 2.25–2.1, 2.0–1.9 (3*m*, 2 H each, 3 CH$_2$(Acb); 1.47, 1.44 (2*s*, 2 Me$_2$C). ^{13}C-NMR (CD$_3$OD): 178.2, 176.3, 175.3, 172.5 (4*s*, 3 CO(amide), COOH); 159.5 (*s*, CO(urethane)); 138.1 (*s*, 1 arom. C); 129.5, 129.1, 128.9 (3*d*, 5 arom. CH); 68.1 (*t*, Ph*C*H$_2$O); 60.5, 57.7, 57.1 (3*s*, 2 C(2)(Aib), C(2)(Acb)); 45.3 (*t*, CH$_2$(Gly)); 31.9 (*t*, 2 CH$_2$(Acb)); 25.4 (*q*, 2 *Me*$_2$C); 16.5 (*t*, CH$_2$(Acb)). ESI-MS: 499 (100, [*M*+Na]$^+$). Anal. calc. for C$_{23}$H$_{32}$N$_4$O$_7$ (476.53): C 57.97, H 6.77, N 11.76; found: C 57.76, H 6.84, N 11.31.

3.3.5. *Z-Gly-Aib-Acb-Aib-Gly-OMe* (**8c**). According to *GP 5*, **7b** (268 mg, 0.653 mmol) and H-Gly-OMe.HCl (79 mg, 0.629 mmol) were treated with HBPyU (243 mg, 0.564 mmol) and DIEA (220 mg, 1.702 mmol) for 0.5 h. CC (AcOEt/MeOH 20:1) gave 255 mg (83%) of **8c**. Colorless solid. M.p. 160.0–161.4°. IR (KBr): 3340*s*, 3280*s*, 3060*m*, 2980*m*, 2950*m*, 1740*s*, 1710*s*, 1685*s*, 1650*s*, 1630*s*, 1550*s*, 1540*s*, 1530*s*, 1505*m*, 1470*m*, 1465*m*,

1455*m*, 1440*m*, 1380*m*, 1365*m*, 1310*m*, 1275*s*, 1240*s*, 1220*m*, 1195*m*, 1170*m*, 1155*m*, 1050*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.52 (*s*, NH); 7.46 (*t*, *J* = 5.8, NH(Gly)); 7.4–7.35 (*m*, 5 arom. H, 1 NH); 6.90 (*s*, NH); 6.31 (*t*-like, NH); 5.14 (*s*, PhC*H*$_2$O); 3.98 (*d*, *J* = 5.8, CH_2(Gly)); 3.75 (*d*, *J* = 5.2, CH_2(Gly)); 3.65 (*s*, MeO); 2.75–2.7, 2.05–1.85 (2*m*, 1:2, 3 CH_2(Acb); 1.55, 1.46 (2*s*, 2 Me_2C). ^{13}C-NMR ($CDCl_3$): 176.5, 175.3, 173.6, 171.0, 170.6 (5*s*, 4 CO(amide), COOMe); 157.8 (*s*, CO(urethane)); 136.4 (*s*, 1 arom. C); 128.6, 128.2, 127.6 (3*d*, 5 arom. CH); 67.2 (*t*, Ph*C*H_2O); 59.2, 57.0, 56.6 (3*s*, 2 C(2)(Aib), C(2)(Acb)); 52.1 (*q*, MeO); 45.8, 41.4 (2*t*, 2 CH_2(Gly)); 30.9 (*t*, 2 CH_2(Acb)); 25.3, 24.7 (2*q*, 2 *Me*$_2$C); 15.4 (*t*, CH_2(Acb)). ESI-MS: 570 (100, $[M+Na]^+$).

3.4. *Z-Gly-Aib-Pro-Aib-Aib-N(Me)Ph* (**8d**). According to *GP 5*, **3** (1.18 g, 4.00 mmol) and H-Pro-Aib-Aib-N(Me)Ph [25b] (1.65 g, 4.40 mmol) in CH_2Cl_2 (20 ml) were treated with HBPyU (1.72 g, 4.00 mmol) and DIEA (1.03 g, 8.00 mmol) for 15 h. CC (CH_2Cl_2/MeOH 20:1) gave 2.15 g (82%) of **8d**. Colorless solid. M.p. 107.6–108.7°. $[\alpha]_D$ = +34.5 (c = 1.04, EtOH). IR (KBr): 3420*m*, 3300*s*, 3060*m*, 2980*m*, 2930*m*, 1725*s*, 1660*s*, 1625*s*, 1595*m*, 1540*s*, 1520*s*, 1495*s*, 1470*m*, 1455*m*, 1410*m*, 1395*m*, 1365*m*, 1280*m*, 1240*s*, 1215*m*, 1170*m*, 1090*m*, 1050*m*, 705*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.57 (*s*, NH); 7.41 (*s*, NH); 7.4–7.15 (*m*, 10 arom. H, 1 NH); 6.14 (br. *s*, NH); 5.10, 5.08 (*AB*, J_{AB} = 12.0, PhC*H*$_2$O); 4.2–4.15 (*m*, CH_2(2)(Pro)); 3.8–3.55 (*m*, CH_2(Gly), 1 H of CH_2(5)(Pro)); 3.38 (*s*, MeN); 3.35–3.2 (*m*, 1 H of CH_2(5)(Pro)); 2.35–2.2, 1.95–1.8, 1.75–1.65 (3*m*, CH_2(3), CH_2(4)(Pro)); 1.60, 1.58, 1.49, 1.43, 1.28 (5*s*, 1:1:1:2:1, 3 Me_2C). ^{13}C-NMR ($CDCl_3$): 175.1, 174.3, 173.3, 171.7, 169.7 (5*s*, 5 CO(amide)); 156.9 (*s*, CO(urethane)); 145.5, 136.5 (2*s*, 2 arom. C); 129.1, 128.5, 128.2, 128.0, 127.2, 126.6 (6*d*, 10 arom. CH); 66.9 (*t*, Ph*C*H_2O); 64.2 (*d*, CH(2)(Pro)); 57.1, 57.0, 56.5 (3*s*, 3 C(2)(Aib)); 48.7 (*t*, CH_2(5)(Pro)); 44.1 (*t*, CH_2(Gly)); 40.1 (*s*, MeN); 28.8, 26.2 (2*t*, CH_2(3), CH_2(4)(Pro)); 27.8, 26.1, 25.8, 25.6, 23.9, 23.6 (6*q*, 3 *Me*$_2$C). ESI-MS: 673 (100, $[M+Na]^+$).

3.5. *Z-Gly-Aib-Pro-Aib-Aib-OH* (**10**). According to *GP 2*, **8d** (1.03 g, 1.58 mmol) was hydrolyzed for 4.5 h. The precipitate was filtered (549 mg of **10**) and the filtrate purified by CC (CH_2Cl_2/MeOH 10:1). Total yield of **10**: 629 mg (70%). Colorless solid. M.p. 192.3–193.6°. $[\alpha]_D$ = +22.4 (c = 1.02, MeOH). IR (KBr): 3460*m*, 3400*m*, 3310*s*, 3290*s*, 3040*m*, 2990*m*, 2940*m*, 1715*s*, 1665*s*, 1650*s*, 1600*s*, 1540*s*, 1520*s*, 1470*m*, 1450*m*, 1425*m*, 1410*m,* 1365*m*, 1310*m*, 1290*m*, 1280*m*, 1250*m*, 1215*m*, 1170*m*, 695*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.53 (*s*, NH); 7.55–7.3 (*m*, 5 arom. H, 2 NH); 7.17 (*s*, NH); 5.04, 5.00 (*AB*, J_{AB} = 12.6, PhC*H*$_2$O); 4.09 (*t*, *J* = 7.8, CH_2(2)(Pro)); 3.85–3.7, 3.7–3.55, 3.55–3.54 (3*m*, 1:2:1, CH_2(Gly), CH_2(5)(Pro)); 2.15–2.0, 1.95–1.7, 1.65–1.45 (3*m*, 1:2:1, CH_2(3), CH_2(4)(Pro)); 1.37, 1.34, 1.32, 1.29 (4*s*, 1:2:2:1, 3 Me$_2$C). ^{13}C-NMR ((D$_6$)DMSO): 175.4, 173.4, 172.3, 171.1, 168.9 (5*s*, 4 CO(amide), COOH); 156.5 (*s*, CO(urethane)); 136.9 (*s*, 1 arom. C); 128.2, 127.7, 127.6 (3*d*, 5 arom. CH); 65.4 (*t*, Ph*C*H$_2$O); 62.8 (*d*, CH(2)(Pro)); 55.6, 54.6 (2*s*, 3 C(2)(Aib)); 47.8 (*t*, CH_2(5)(Pro)); 42.7 (*t*, CH_2(Gly)); 28.2, 25.5 (2*t*, CH_2(3), CH_2(4)(Pro)); 25.9, 25.4, 24.9, 24.1, 24.0, 23.9 (6*q*, 3 *Me*$_2$C). ESI-MS: 584 (100, $[M+Na]^+$). Anal. calc. for $C_{27}H_{39}N_5O_8 \cdot 1.5H_2O$ (588.66): C 55.09, H 7.19, N 11.90; found: C 54.99, H 7.23, N 11.88.

Suitable crystals for the X-ray crystal-structure determination were grown from MeOH.

3.6. *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Phe-OMe* (**8e**). 3.6.1. *Z-Gly-Aib-Phe-OMe*. According to *GP 5*, a mixture of Z-Gly-Aib-OH (**3**) [25] (1.03 g, 3.51 mmol) and H-Phe-OMe·HCl (834 mg, 3.87 mmol) in CH_2Cl_2 (5 ml) was treated with PyBOP (1.68 g, 3.52 mmol) and DIEA (1.34 g, 10.65 mmol). CC (AcOEt/hexane 3:1) gave 1.36 g (85%) Z-Gly-Aib-Phe-OMe. Colorless solid. M.p. 150–158.7°. $[\alpha]_D$ = +6.6 (c = 1.01, EtOH). IR (KBr): 3380*m*, 3260*m*, 3070*m*, 1745*s*, 1710*s*, 1680*s*, 1635*s*, 1555*s*, 1525*m*, 1380*m*, 1275*m*, 1250*m*, 1215*m*, 1205*m*, 1180*m*, 1160*m*, 1110*w*, 1080*w*, 1030*w*, 695*m*. ^{1}H-NMR ($CDCl_3$): 7.35–7.2 (*m*, 8 arom. H); 7.15–7.1 (*m*, 2 arom. H); 6.67 (br. *d*, *J* = 6.7, NH); 6.54, 5.37 (2br. *s*, 2 NH);

5.13 (*s*, PhC*H*$_2$O); 4.9–4.8 (*ABX*, CH(2)(Phe)); 3.78 (*d*, *J* = 5.6, CH$_2$(Gly)); 3.72 (*s*, MeO); 3.2–3.05 (*ABX*, J_{AB} = 13.9, PhC*H*$_2$); 1.48 (*s*, Me$_2$C). ^{13}C-NMR ($CDCl_3$): 173.7, 171.9, 168.6 (3*s*, 2 CO(amide), COOMe); 156.7 (*s*, CO(urethane)); 136.1, 135.9 (2*s*, 2 arom. C); 129.3, 128.52, 128.48, 128.2, 128.0, 127.0 (6*d*, 10 arom. CH); 67.2 (*t*, Ph*C*H$_2$O); 57.2 (*s*, C(2)(Aib)); 53.4 (*q*, MeO); 52.3 (*d*, CH(2)(Phe)); 44.9 (*t*, CH$_2$(Gly)); 37.7 (*t*, Ph*C*H$_2$); 25.0, 24.9 (2*q*, *Me*$_2$C). ESI-MS: 478 (7, [*M*+Na]$^+$). Anal. calc. for $C_{24}H_{29}N_3O_6$ (455.50): C 63.29, H 6.42, N 9.23; found: C 62.99, H 6.64, N 8.99.

3.6.2. *H-Gly-Aib-Phe-OMe* (**12**). According to *GP 3*, Z-Gly-Aib-Phe-OMe (158.6 mg, 0.348 mmol) was deprotected: 110 mg (98%) of **12**. Colorless oil. IR ($CDCl_3$): 3420*m*, 3310*m*, 2930*m*, 1740*m*, 1685*s*, 1660*s*, 1635*s*, 1600*m*, 1540*s*, 1510*s*, 1495*s*, 1450*m*, 1435*m*, 1385*m*, 1360*m*, 1330*m*, 1275*m*, 1175*m*, 690*m*. ^{1}H-NMR ($CDCl_3$): 7.64 (*s*, NH); 7.3–7.1 (*m*, 5 arom. H, 1 NH); 4.9–4.8 (*ABX*, CH(2)(Phe)); 3.71 (*s*, MeO); 3.26 (*s*, CH$_2$(Gly)); 3.2–3.05 (*ABX*, J_{AB} = 13.9, PhC*H*$_2$); 1.51, 1.49 (2*s*, Me$_2$C). ^{13}C-NMR ($CDCl_3$): 174.0, 172.8, 172.0 (3*s*, 2 CO(amide), COOMe); 136.0 (*s*, 1 arom. C); 129.3, 128.3, 126.9 (3*d*, 5 arom. CH); 56.8 (*s*, C(2)(Aib)); 53.3 (*d*, CH(2)(Phe)); 52.2 (*q*, MeO); 44.9 (*t*, CH$_2$(Gly)); 37.6 (*t*, Ph*C*H$_2$); 25.0 (*q*, *Me*$_2$C). ESI-MS: 665 (46, [2*M*+Na]$^+$), 643 (100 [2*M*+1]$^+$), 633 (82, [2*M*-MeOH+Na]$^+$), 611 (26, [2*M*-OMe]$^+$), 344 (88, [*M*+Na]$^+$), 322 (21, [*M*+1]$^+$).

3.6.3. *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Phe-OMe* (**8e**). According to *GP 5*, a mixture of Z-Gly-(*R*,*S*)-Phe(2Me)-OH (**11**) [25a] (734 mg, 1.98 mmol) and **12** (700 mg, 2.18 mmol) in CH_2Cl_2 (10 ml) was treated with PyBOP (949 mg, 1.98 mmol) and DIEA (533 mg, 4.12 mmol). CC (2×, AcOEt/MeOH 20:1) and PLC (AcOEt/MeOH 10:1) gave 623 mg (*S*,*S*)-**8e** and 586 mg (*R*,*S*)-**8e**; total yield: 1.21 mg (91%).

*Z-Gly-(*S*)-Phe(2Me)-Gly-Aib-Phe-OMe* ((*S*,*S*)-**8e**). Colorless solid. M.p. 162.5–164.1°. $[\alpha]_D$ = –69.0 (c = 1.01, EtOH). IR (KBr): 3410*m*, 3280*s*, 1745*s*, 1730*s*, 1670*s*, 1660*s*, 1535*s*, 1455*m*, 1385*m*, 1360*m*, 1325*m*, 1280*m*, 1230*s*, 1190*m*, 1185*m*, 1165*m*, 1150*m*, 1110*w*,

1080*w*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.4–7.05 (*m*, 15 arom. H, 3 NH); 6.49 (*s*, NH); 5.80 (*t*-like, NH); 5.05, 4.98 (*AB*, J_{AB} = 12, PhC*H*$_2$O); 4.8–4.7 (*ABX*, CH(2)(Phe)); 3.9–3.65 (*m*, 2 CH_2(Gly)); 3.60 (*s*, MeO); 3.29, 3.03 (*AB*, J_{AB} = 13.6, PhC*H*$_2$); 3.2–3.05 (*m*, PhC*H*$_2$); 1.48, 1.44, 1.40 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.3, 175.0, 173.2, 170.7, 170.0 (5*s*, 4 CO(amide), COOMe); 157.3 (*s*, CO(urethane)); 136.8, 136.1, 135.3 (3*s*, 3 arom. C); 130.5, 129.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.2, 126.8 (9*d*, 15 arom. CH); 67.3 (*t*, PhCH_2O); 59.6, 57.0 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 54.1 (*d*, CH(2)(Phe)); 52.5 (*q*, MeO); 45.4, 44.3 (2*t*, 2 CH_2(Gly)); 36.9, 30.7 (2*t*, 2 PhCH_2); 25.9, 24.3, 22.7 (3*q*, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 696 (100, $[M+Na]^+$). Anal. calc. for $C_{36}H_{43}N_5O_8 \cdot H_2O$ (691.78): C 62.50, H 6.56, N 10.12; found: C 62.43, H 6.30, N 10.07.

Suitable crystals for the X-ray crystal-structure determination were grown from AcOEt/hexane by slow evaporation of the solvent.

*Z-Gly-(*R*)-Phe(2Me)-Gly-Aib-Phe-OMe* ((*R*,*S*)-**8e**). Colorless solid. M.p. 116.4–118.2°. $[\alpha]_D$ = +67.5 (c = 1.05, EtOH). IR (KBr): 3380*m*, 3280*s*, 1730*s*, 1680*s*, 1670*s*, 1660*s*, 1540*s*, 1530*s*, 1455*m*, 1440*m*, 1410*m*, 1390*m*, 1365*m*, 1345*m*, 1310*m*, 1275*m*, 1230*m*, 1195*m*, 1175*m*, 1150*m*, 1120*w*, 1080*w*, 1045*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 8.35 (br. *s*, NH); 7.65 (*s*, NH); 7.42 (*d*, *J* = 7.9, NH); 7.4–7.05 (*m*, 15 arom. H); 7.00 (*s*, NH); 6.18 (br. *s*, NH); 5.12, 5.00 (*AB*, J_{AB} = 12.3, PhC*H*$_2$O); 4.65–4.55 (*m*, CH(2)(Phe)); 4.0–3.6 (*m*, 2 CH_2(Gly)); 3.47, 3.10 (*AB*, J_{AB} = 13.7, PhC*H*$_2$); 3.24 (*s*, MeO); 3.25–2.95 (*m*, PhC*H*$_2$); 1.43, 1.38, 1.26 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 176.9, 176.4, 172.3, 171.0, 169.9 (5*s*, 4 CO(amide), COOMe); 157.0 (*s*, CO(urethane)); 136.7, 136.4, 136.2 (3*s*, 3 arom. C); 131.1, 129.0, 128.5, 128.4, 128.2, 128.1, 126.8, 126.6 (8*d*, 15 arom. CH); 67.1 (*t*, PhCH_2O); 59.4, 57.0 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 54.1 (*d*, CH(2)(Phe)); 52.0 (*q*, MeO); 45.5, 44.3 (2*t*, 2 CH_2(Gly)); 39.5, 37.2 (2*t*, 2 PhCH_2); 27.0, 23.5 (2*q*, 1:2, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 696

(100, [*M*+Na]$^+$). Anal. calc. for $C_{36}H_{43}N_5O_8$ (673.76): C 64.18, H 6.43, N 10.39; found: C 63.91, H 6.33, N 10.53.

3.7. *Z-Gly-(*R,S*)-Phe(2Me)-Gly-Aib-Aib-N(Me)Ph* (**8f**). According to *GP 5*, a mixture of **11** (100 mg, 0.270 mmol) and H-Gly-Aib-Aib-N(Me)Ph [25a] (99 mg, 0.296 mmol) in CH_2Cl_2 (2 ml) was treated with PyBOP (129 mg, 0.270 mmol) and DIEA (85 mg, 0.658 mmol): 152 mg (82%) of **8f**. Colorless solid. M.p. 191.9–192.8°. IR (KBr): 3410*m*, 3300*m*, 1725*m*, 1680*s*, 1665*s*, 1650*s*, 1640*s*, 1595*m*, 1535*s*, 1495*m*, 1455*m*, 1395*m*, 1375*m*, 1365*m*, 1270*m*, 1250*m*, 1240*m*, 1095*m*, 710*m*. ^{1}H-NMR ($CDCl_3$): 7.86 (br. *s*, NH); 7.4–7.05 (*m*, 15 arom. H, 2 NH); 6.83, 6.54 (2br. *s*, 2 NH); 5.08, 5.02 (*AB*, J_{AB} = 12.2, PhCH_2O); 3.8–3.6 (*m*, 2 CH_2(Gly)); 3.23 (*s*, MeN); 3.23, 2.98 (*AB*, J_{AB} = 13.6, PhCH_2); 1.49, 1.46, 1.27 (3*s*, 3:1:1, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.6, 175.2, 174.0, 170.8, 169.2 (5*s*, 5 CO(amide)); 157.3 (*s*, CO(urethane)); 145.3, 136.2, 135.6 (3*s*, 3 arom. C); 130.5, 129.1, 128.4, 128.2, 128.1, 127.9, 127.0, 126.9 (8*d*, 15 arom. CH); 67.0 (*t*, Ph*C*H_2O); 59.3, 57.1 (2*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 45.4, 44.8, 40.7 (3*t*, 2 CH_2(Gly), Ph*C*H_2); 40.3 (*q*, MeN); 25.91, 25.88, 24.9, 22.7 (4*q*, 1:2:1:1, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 725 (8, [*M*+K]$^+$), 709 (100, [*M*+Na]$^+$), 580 (5, [*M*–N(Me)Ph]$^+$). Anal. calc. for $C_{37}H_{46}N_6O_7$ (686.81): C 64.71, H 6.75, N 12.24; found: C 64.90, H 6.89, N 12.40.

Suitable crystals for the X-ray crystal-structure determination were grown from AcOEt/hexane by slow evaporation of the solvent.

3.8. *Z-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Phe-OMe* (**8g**). 3.8.1. *Z-Pro-Aib-Phe-OMe*. According to *GP 5*, a mixture of Z-Pro-Aib-OH [25b] (1.14 g, 3.40 mmol) and H-Phe-OMe·HCl (808 mg, 3.75 mmol) in CH_2Cl_2 (6 ml) was treated with PyBOP (1.63 g, 3.40 mmol) and DIEA (1.32 g, 10.23 mmol). CC (AcOEt/hexane 3:1) gave 1.33 g (79%) Z-Pro-Aib-Phe-OMe. Colorless solid. M.p. 169.7–170.4°. $[\alpha]_D$ = –23.8 (c = 0.817, EtOH). IR (KBr): 3380*m*, 3280*m*, 1745*s*, 1690*s*, 1665*s*, 1640*s*, 1550*m*, 1525*m*, 1455*m*, 1435*s*, 1355*m*, 1240*m*,

1215*m*, 1205*m*, 1180*m*, 1170*m*, 1120*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.35–7.1 (*m*, 10 arom. H, 0.8 NH); 6.86 (br. *s*, NH); 6.40 (br. *s*, 0.2 NH); 5.2–5.1 (*m*, PhC*H*$_2$O); 4.8–4.75, 4.25–4.2 (2*m*, CH(2)(Phe), CH(2)(Pro)); 3.68 (*s*, MeO); 3.6–3.4 (*m*, CH_2(5)(Pro)); 3.2–3.0 (*ABX*, J_{AB} = 13.9, PhC*H*$_2$); 2.25–1.25 (*m*, CH_2(3), CH_2(4)(Pro)); 1.44, 1.26 (2br. *s*, Me_2C). ^{13}C-NMR ($CDCl_3$): 173.7, 171.9 (2*s*, 2 CO(amide), COOMe); 156.1 (*s*, CO(urethane)); 136.3 (*s*, 2 arom. C); 129.2, 128.4, 128.3, 128.1, 127.8, 126.8 (6*d*, 10 arom. CH); 67.2 (*t*, Ph*C*H$_2$O); 61.0 (*d*, CH(2)(Pro)); 57.2 (*s*, C(2)(Aib)); 53.6 (*d*, CH(2)(Phe)); 52.0 (*s*, MeO); 47.0 (*t*, CH_2(5)(Pro)); 37.8 (*t*, Ph*C*H$_2$); 28.4, 24.8 (2*t*, CH_2(3), CH_2(4)(Pro)); 25.5, 24.8 (2*q*, *Me*$_2$C). ESI-MS: 518 (100, [*M*+Na]$^+$). Anal. calc. for $C_{27}H_{33}N_3O_6$ (495.57): C 65.44, H 6.71, N 8.48; found: C 65.49, H 6.97, N 8.54.

3.8.2. *H-Pro-Aib-Phe-OMe* (**13**). According to *GP 3*, Z-Pro-Aib-Phe-OMe (1.15 g, 2.32 mmol) in MeOH (25 ml) in the presence of Pd/C (113 mg) was deprotected (2 h): 842 mg (84%) **13**. Colorless oil. $[\alpha]_D$ = +3.6 (c = 1.24, $CHCl_3$). IR ($CHCl_3$): 3280*m*, 3020*m*, 3000*s*, 2980*m*, 1740*s*, 1670*s*, 1510*s*, 1455*m*, 1440*m*, 1390*m*, 1360*m*, 1215*m*, 1180*m*, 850*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.89 (*s*, NH); 7.41 (*d*, *J* = 7.5, NH); 7.3–7.15 (*m*, 5 arom. H); 4.8–4.75, 3.7–3.65 (2*m*, CH(2)(Pro), CH(2)(Phe)); 3.69 (*s*, MeO); 3.2–2.9 (*m*, CH_2(5)(Pro), PhC*H*$_2$, NH(Pro)); 2.15–2.05, 1.9–1.85, 1.75–1.65 (3*m*, 1:1:2, CH_2(3), CH_2(4)(Pro)); 1.47, 1.45 (2*s*, Me_2C). ^{13}C-NMR ($CDCl_3$): 175.2, 174.2, 172.1 (3*s*, 2 CO(amide), COOMe); 136.3 (*s*, 1 arom. C); 129.3, 128.4, 126.9 (3*d*, 5 arom. CH); 60.7 (*d*, CH(2)(Pro)); 56.9 (*s*, C(2)(Aib)); 53.5 (*d*, CH(2)(Phe)); 52.2 (*s*, MeO); 47.2 (*t*, CH_2(5)(Pro)); 37.7 (*t*, Ph*C*H$_2$); 30.6, 26.0 (2*t*, CH_2(3), CH_2(4)(Pro)); 25.2, 25.1 (2*q*, *Me*$_2$C). CI-MS: 363 (21), 362 (100, [*M*+1]$^+$).

3.8.3. *Z-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Phe-OMe* (**8g**). According to *GP 5*, a mixture of **11** (374.5 mg, 1.01 mmol) and **13** (400 mg, 1.11 mmol) in CH_2Cl_2 (10 ml) was treated with TBTU (326.2 mg, 1.02 mmol) and DIEA (301.8 mg, 2.34 mmol) for 16 h. CC (4×,

AcOEt/MeOH 20:1) gave 193.9 mg (*S*,*S*)-**8g** and 319.8 mg (*R*,*S*)-**8g**; total yield: 513.7 mg (71%).

*Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OMe* ((*S*,*S*,*S*)-**8g**). Colorless lacquer. M.p. 59.1–60.7°. $[\alpha]_D$ = –17.6 (c = 1.03, EtOH). IR (KBr): 3300*m*, 2940*m*, 1745*s*, 1740*s*, 1730*s*, 1720*s*, 1670*s*, 1660*s*, 1635*s,* 1625*s*, 1565*m*, 1540*s*, 1520*s*, 1505*s*, 1460*m*, 1455*m*, 1410*m*, 1385*m*, 1240*s*, 1170*m*, 1050*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.49 (*d*, *J* = 8.1, NH); 7.45–7.05 (*m*, 15 arom. H, NH); 6.92 (*s*, NH); 5.71 (*t*-like, NH); 5.16, 5.10 (*AB*, J_{AB} = 12.2, PhCH_2O); 4.8–4.7 (*m*, CH(2)(Phe)); 4.41 (*t*, CH(2)(Pro)); 3.9–3.7 (*AB* of *ABX*, CH_2(Gly)); 3.61 (*s*, MeO); 3.4–3.1, 3.1–2.95 (2*m*, 1:1, 2 PhCH_2), CH_2(5)(Pro)); 2.25–2.1, 1.85–1.65, 1.65–1.5 (3*m*, 1:2:1, CH_2(3), CH_2(4)(Pro)); 1.52, 1.50, 1.34 (3*s*, Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.1, 172.2, 171.6, 171.1, 169.0 (5*s*, 4 CO(amide), COOMe); 156.8 (*s*, CO(urethane)); 137.1, 136.0, 134.5 (3*s*, 3 arom. C); 130.2, 129.2, 128.9, 128.6, 128.5, 128.2, 127.7, 126.5 (8*d*, 15 arom. CH); 67.4 (*t*, Ph*C*H_2O); 63.6 (*d*, C(2)(Pro)); 60.1, 57.1 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 53.9 (*d*, CH(2)(Phe)); 52.0 (*q*, MeO); 48.6 (*t*, CH_2(5)(Pro)); 44.8 (*t*, CH_2(Gly)); 43.0, 37.9 (2*t*, 2 Ph*C*H_2); 28.3, 26.0 (2*t*, CH_2(3), CH_2(4)(Pro)); 26.7, 24.4, 24.0 (3*q*, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 736 (100, $[M+Na]^+$).

*Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OMe* ((*R*,*S*,*S*)-**8g**). Colorless solid. M.p. 165.5–166.5°. $[\alpha]_D$ = +68.9 (c = 1.04, EtOH). IR (KBr): 3400*s*, 3060*m*, 3030*m*, 2980*m*, 2940*m*, 1750*s*, 1730*s*, 1655*s*, 1625*s*, 1545*s*, 1535*s*, 1500*m*, 1455*m*, 1445*m*, 1405*m*, 1385*m*, 1375*m*, 1365*m*, 1305*m*, 1280*m*, 1240*s*, 1170*m*, 1160*m*, 1130*w*, 1100*m*, 1080*m*, 1045*m*, 1030*m*, 1000*m*, 740*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 7.50 (*d*, *J* = 8.1, NH); 7.39 (*s*, NH); 7.4–7.0 (*m*, 15 arom. H); 6.85 (*s*, NH); 5.70 (br. *s*, NH); 5.08 (*s*, PhCH_2O); 4.75–4.65 (*m*, CH(2)(Phe)); 4.37 (*t*-like, CH(2)(Pro)); 4.0–3.8 (*AB* of *ABX*, CH_2(Gly)); 3.75–3.65, 3.35–3.2 (2*m*, CH_2(5)(Pro)); 3.61 (*s*, MeO); 3.42, 3.17 (*AB*, J_{AB} = 13.8, PhCH_2); 3.25–3.1, 3.1–2.95 (2*m*, PhCH_2); 2.2–2.05, 1.95–1.8, 1.8–1.6 (3*m*, 1:1:2, CH_2(3), CH_2(4)(Pro)); 1.46, 1.39, 1.26 (3*s*, Me_2C,

Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 175.3, 172.5, 172.4, 171.2, 169.3 (5*s*, 4 CO(amide), COOMe); 156.8 (*s*, CO(urethane)); 136.8, 136.6, 136.1 (3*s*, 3 arom. C); 131.1, 129.1, 128.6, 128.3, 128.22, 128.17, 128.1, 126.8, 126.6 (9*d*, 15 arom. CH); 67.2 (*t*, Ph*C*H_2O); 63.7 (*d*, CH(2)(Pro)); 59.1, 57.1 (2*s*, C(2)(Aib), C(2)(Phe(2Me))); 53.6 (*d*, CH(2)(Phe)); 52.0 (*q*, MeO); 48.7 (*t*, CH_2(5)(Pro)); 44.4 (*t*, CH_2(Gly)); 40.9, 37.8 (2*t*, 2 Ph*C*H_2); 28.5, 26.0 (2*t*, CH_2(3), CH_2(4)(Pro)); 27.0, 24.1, 21.1 (3*q*, *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 736 (100, $[M+Na]^+$), 714 (10, $[M+1]^+$), 535 (6, $[M$-PheOMe$]^+$).

Suitable crystals for the X-ray crystal-structure determination were grown from AcOEt/MeOH by slow evaporation of the solvent.

3.9. *Z-Gly-(*R,S*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* (**8h**). According to *GP 5*, a mixture of **11** (1.25 g, 3.36 mmol) and H-Pro-Aib-Aib-N(Me)Ph [25b] (1.40 g, 3.73 mmol) in CH_2Cl_2 (30 ml) was treated with TBTU (1.20 g, 3.74 mmol), HOBt (910 mg, 6.73 mmol), and DIEA (916 mg, 7.09 mmol) for 18 h. CC (CH_2Cl_2/MeOH 15:1) gave 1.76 g (72%) **8h**. Separation of 815.5 mg of the mixture of the diastereoisomers by PLC (AcOEt/MeOH 20:1, 5× developed) led to 224.6 mg of (*S*,*S*)-**8h** and 470.6 mg of (*R*,*R*)-**8h**.

*Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* ((*S*,*S*)-**8h**). Colorless solid. M.p. 92.4–93.9°. $[\alpha]_D$ = +14.0 (c = 0.57, EtOH). IR (KBr): 3310*s*, 2980*m*, 2930*m*, 1730*s*, 1680*s*, 1660*s*, 1630*s,* 1595*m*, 1545*s*, 1540*s*, 1530*s*, 1495*s*, 1465*m*, 1455*m*, 1405*m*, 1390*s*, 1360*m*, 1280*m*, 1240*s*, 1200*m*, 1160*m*, 1090*m*, 1050*m*, 740*m*, 700*s*. ^{1}H-NMR ($CDCl_3$): 7.52 (*s*, NH); 7.35–7.05 (*m*, 15 arom. H, 2 NH); 6.29 (br. *s*, NH); 5.12, 5.08 (*AB*, J_{AB} = 12.3, PhCH_2O); 4.22 (*t*, *J* = 8.3, CH(2)(Pro)); 3.8–3.55 (*AB* of *ABX*, J_{AB} = 17.2, CH_2(Gly)); 3.38 (*s*, MeN); 3.2–3.0 (*m*, CH_2(5)(Pro)); 2.91 (*s*, PhCH_2); 2.3–2.15, 1.85–1.7, 1.7–1.4 (3*m*, 1:1:2, CH_2(3), CH_2(4)(Pro)); 1.60, 1.57, 1.47, 1.45, 1.40 (5*s*, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 174.7, 174.1, 171.8, 171.6, 169.8 (5*s*, 5 CO(amide)); 157. (*s*, CO(urethane)); 146.1, 136.4, 134.6 (3*s*, 3 arom. C); 130.1, 129.0, 128.8, 128.6, 128.3, 128.1, 127.6, 127.2, 126.6 (9*d*, 15 arom. CH);

67.0 (*t*, Ph*C*H_2O); 64.4 (*d*, C(2)(Pro)); 60.3, 57.2, 57.0 (3*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 48.6, 44.6, 43.6 (3*t*, CH_2(Gly), CH_2(5)(Pro), PhCH_2); 40.1 (*q*, MeN); 28.6, 26.2 (2*t*, CH_2(3), CH_2(4)(Pro)); 27.8, 26.4, 25.4, 24.3, 23.7 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 749 (100, [*M*+Na]$^+$). Anal. calc. for $C_{40}H_{50}N_6O_7 \cdot 0.5H_2O$ (735.88): C 65.29, H 6.99, N 11.42; found: C 65.28, H 7.17, N 11.15.

*Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph* ((*R*,*S*)-**8h**). Colorless solid. M.p. 168.7–170.2°. $[\alpha]_D$ = +114 (c = 0.51, EtOH). IR (KBr): 3300*s*, 3060*w*, 3030*w*, 2980*w*, 2940*w*, 1725*s*, 1660*s*, 1625*s*, 1595*m*, 1540*s*, 1495*m*, 1465*m*, 1455*m*, 1410*m*, 1395*m*, 1375*m*, 1360*m*, 1280*m*, 1240*m*, 1160*m*, 1135*m*, 1090*m*, 1050*m*, 705*s*. ^{1}H-NMR ($CDCl_3$): 7.44 (*s*, NH); 7.35–7.05 (*m*, 15 arom. H, 2 NH); 5.95 (br. *s*, NH); 5.09 (*s*, PhCH_2O); 4.23 (*t*, *J* = 8.3, CH(2)(Pro)); 3.9–3.6 (*AB* of *ABX*, J_{AB} = 17, CH_2(Gly)); 3.7–3.6, 3.3–3.1 (2*m*, CH_2(5)(Pro)); 3.37, 3.08 (*AB*, J_{AB} = 13.7, PhCH_2); 3.29 (*s*, MeN); 2.3–2.15, 1.95–1.85, 1.85–1.6 (3*m*, 1:1:2, CH_2(3), CH_2(4)(Pro)); 1.54, 1.45, 1.39, 1.17 (4*s*, 1:1:2:1, 2 Me_2C, Me(Phe(2Me))). ^{13}C-NMR ($CDCl_3$): 174.8, 173.9, 173.1, 171.3, 169.6 (5*s*, 5 CO(amide)); 156.8 (*s*, CO(urethane)); 145.9, 136.5, 136.2 (3*s*, 3 arom. C); 131.2, 128.9, 128.6, 128.3, 128.2, 127.2, 126.8, 126.6 (8*d*, 15 arom. CH); 67.1 (*t*, Ph*C*H_2O); 64.4 (*d*, CH(2)(Pro)); 58.9, 57.1 (2*s*, 2 C(2)(Aib), C(2)(Phe(2Me))); 48.8 (*t*, CH_2(5)(Pro)); 44.2 (*t*, CH_2(Gly)); 40.7 (*t*, Ph*C*H_2); 40.1 (*q*, MeN); 28.7, 26.2 (2*t*, CH_2(3), CH_2(4)(Pro)); 27.7, 26.3, 25.6, 23.7, 20.9 (5*q*, 2 *Me*$_2$C, Me(Phe(2Me))). ESI-MS: 749 (100, [*M*+Na]$^+$), 620 (7, [*M*-N(Me)Ph]$^+$).

Suitable crystals for the X-ray crystal-structure determination were grown from AcOEt/MeOH/hexane by slow evaporation of the solvent.

4. *X-Ray Crystal-Structure Determination of* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (see *Table 4* and *Figs. 1 – 7*)[9]). The measurements were made using graphite-

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[9]) CCDC-989272–989278 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data

monochromated MoK_α radiation (λ 0.7107 Å) on a *Rigaku AFC5R* diffractometer fitted to a 12-kW rotating-anode generator. The intensities were corrected for *Lorentz* and polarization effects. Empirical absorption corrections based on azimuthal scans of several reflections [45] were applied in the cases of **8f** and (*R*,*S*,*S*)-**8g**. Equivalent reflections, other than *Friedel* pairs for structures in non-centrosymmetric space groups, were merged. The data collection and refinement parameters are given in *Table 4*, and views of the molecules are shown in *Figs. 1 – 7*. Each structure was solved by direct methods using SHELXS86 [46] for **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, and **10**, which revealed the positions of all non-H-atoms, and *SnB* [47][10] for (*R*,*S*)-**8h**, which revealed the positions of most of the non-H-atoms. In the latter case, the remaining non-H atoms were located in a subsequent difference electron density map. For all structures, the non-H-atoms were refined anisotropically. Unless indicated otherwise fro individual structures below, H-atoms on heteroatoms were generally placed in the positions indicated by difference electron density maps and their positions were allowed to refine together with individual isotropic displacement parameters. All other H-atoms were placed in geometrically calculated positions and refined by using a riding model, with $U_{iso}(H)$ = $1.2U_{eq}$(parent atom) ($1.5U_{eq}$ for Me groups).

In the case of **6a**, the Ph ring of the middle benzyl group of the molecule is disordered over two orientations. The site occupation factor for the major conformation refined to 0.645(19). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighbouring atoms within and between each

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Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[10]) We are grateful to *R. Miller* and *C. Weeks* of The *Hauptman-Woodward* Medical Research Institute, Buffalo, who carried out the solution of the structure using what was, at the time in 1996, a new, unreleased version of their program, SnB. Without their assistance, this structure determination would not nave been successful.

conformation of the disordered ring were restrained to have similar atomic displacement parameters. There are disordered solvent molecules present in the crystal lattice, and these lie across centres of inversion, so that the ratio of peptide to solvent molecules is 2:1. The solvent appears to be a hexane molecule which has two orientations, although the end atoms in one orientation may be further disordered. As the disorder could not be modelled adequately, the contribution of the solvent molecules to the intensity data was removed by using the SQUEEZE routine [48] of the PLATON program [49]. Omission of the solvent molecules leaves two cavities of 217 $Å^3$ per unit cell. The number of electrons contributing to each void in the structure was calculated by the SQUEEZE routine to be approximately 41 e, although this may be an underbound. Allowing for one hexane molecule per cavity yields 50 e and this assumption was used in the subsequent calculation of the empirical formula, formula weight, density, linear absorption coefficient and F(000).

In the case of (*S*,*S*)-**8e**, the terminal benzyl group is disordered over two orientations with a site occupation factor for the major conformation of 0.669(5). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighbouring atoms within and between each conformation of the disordered group were restrained to have similar atomic displacement parameters. The terminal methyl ester group might also be slightly disordered, because the atomic displacement parameters of these atoms, particularly O(24), are large. However the disorder could not be resolved reasonably and average positions were used for the atoms of this region of the molecule. As a result the C(24)=O(24) bond appears to be somewhat shorter than it should be. The asymmetric unit also contains two sites which are partially occupied by water molecules. Initial refinement of the site occupation factors of these molecules gave values close to 0.5 and in the final refinement the site occupation factors of the water molecules were set to 0.5. H-atoms were not included for the water molecules.

The crystals of **8f** rapidly lost included solvent on standing in air. The asymmetric unit contains one peptide molecule plus approximately one third of a highly disordered hexane molecule which sits across a centre of inversion. As the disorder could not be modelled adequately, the contribution of the solvent molecules to the intensity data was removed by using the SQUEEZE routine of the PLATON program. Omission of the solvent molecules leaves four cavities of 128 $Å^3$ per unit cell. The number of electrons contributing to each void in the structure was calculated by the SQUEEZE routine to be approximately 31 e. Allowing for two thirds of a hexane molecule per cavity yields 30 e, which leads to a peptide:hexane ratio in the structure of 3:1 and this assumption was used in the subsequent calculations. The amide H-atoms were placed in geometrically calculated positions and refined as described above for riding H-atoms.

In the case of (*R*,*S*,*S*)-**8g**, the asymmetric unit contains one peptide molecule, one AcOEt molecule, and one partially occupied site for a H_2O molecule. The site occupation factor for the O-atom of H_2O was initially refined and then fixed at 0.5. The H-atoms of the H_2O molecule were included in the positions obtained from a difference electron density map and then constrained to ride on the parent O-atom with $U_{iso}(H) = 1.5U_{eq}(O)$.

The asymmetric unit of (*R*,*S*)-**8h** contains two peptide, one hexane, and one half of a H_2O molecule, where the latter sits on a two-fold axis. One of the peptide molecules has a disordered Ph ring in the Z group. Two sets of positions were defined for the atoms of this Ph ring and the site occupation factor of the major conformation of the ring refined to 0.504(1). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, the C–C bonds were restrained to 1.395(5) Å, the two conformations of the ring were restrained to be planar, and neighbouring atoms within and between each conformation of the disordered Ph ring were restrained to have similar atomic displacement parameters. The amide H-atoms were placed in geometrically calculated

positions and refined as described above for riding H-atoms. The position of the symmetry-unique water H-atom was refined with $U_{iso}(H) = 1.5U_{eq}(O)$.

In the case of **10**, the asymmetric unit contains one molecule of the peptide plus a disordered molecule of MeOH. The site occupation factor of the major orientation of the MeOH molecule refined to 0.659(14). Neighbouring atoms within and between each conformation of the disordered MeOH molecule were restrained to have similar atomic displacement parameters. The amide and peptide hydroxy H-atoms were placed in geometrically calculated positions and refined as described above for riding H-atoms; for the hydroxy H-atom $U_{iso}(H) = 1.5U_{eq}(O)$. The hydroxy H-atoms of the MeOH molecules were not included in the model.

The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the case of **6a** and (*R*,*S*)-**8h**. Neutral atom scattering factors for non-H-atoms were taken from [50], and the scattering factors for H-atoms were taken from [51]. Anomalous dispersion effects were included in F_c [52]; the values for f' and f'' were those of [53]. The values of the mass attenuation coefficients are those of [54]. All refinements were performed using SHELXL-2013 [55].

Table 4. *Crystallographic Data for Compounds* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10**

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Legends

Fig. 1. *ORTEP Plot* [32] *of the molecular structure of the tetrapeptide* **6a** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity and only the major conformation of the disordered central benzyl ring is shown, solvent molecule not included)

Fig. 2. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **8a** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity)

Fig. 3. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **8f** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecule not included)

Fig. 4. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* (*S*,*S*)-**8e** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity and only the major conformation of the disordered terminal benzyl group is shown, water molecules not included)

Fig. 5. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* (*R*,*S*,*S*)-**8g** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecules not included)

Fig. 6. *ORTEP Plot* [32] *of the molecular structure of one of the two symmetry-independent molecules of the pentapeptide* (*R*,*S*)-**8h** (50% probability ellipsoids, arbitrary

numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecules not included)

Fig. 7. *ORTEP Plot* [32] *of the molecular structure of the pentapeptide* **10** (50% probability ellipsoids, arbitrary numbering of atoms, H-atoms bonded to C-atoms omitted for clarity, solvent molecule not included)

Table 1. *^{13}C-NMR Chemical Shifts of C(β) and C(γ) of the Pro Residue in Pro-Containing Pentapeptides*

Table 2. *Torsion Angles ω, ϕ,* and *ψ of the Backbone of the Pentapeptides* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** *in the Crystal* (Amino Acid (*i*) = Gly(1))

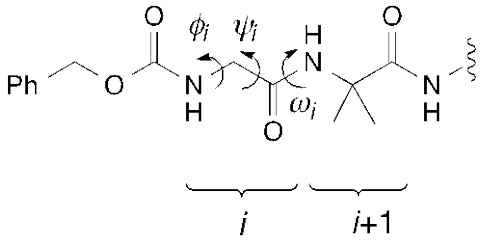
Table 3. *Intramolecular H-Bonds of Compounds* **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (atom numbering refers to *Figs. 1 – 7*)

Table 4. *Crystallographic Data for Compounds* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10**

Table 1. *^{13}C-NMR Chemical Shifts of C(β) and C(γ) of the Pro Residue in Pro-Containing Pentapeptides*

Peptide	Solvent	C(*β*) [ppm]	C(*γ*) [ppm]
Z-Gly-Aib-Pro-Aib-Aib-N(Me)Ph (**8d**)	$CDCl_3$	28.8	26.2
Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Phe-OMe ((*R*,*S*,*S*)-**8g**)	$CDCl_3$	28.5	26.0
Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Phe-OMe ((*S*,*S*,*S*)-**8g**)	$CDCl_3$	28.3	26.0
Z-Gly-(*R*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph ((*R*,*S*)-**8h**)	$CDCl_3$	28.7	26.3
Z-Gly-(*S*)-Phe(2Me)-Pro-Aib-Aib-N(Me)Ph ((*S*,*S*)-**8h**)	$CDCl_3$	28.6	26.2
Z-Gly-Aib-Pro-Aib-Aib-OH (**10**)	(D_6)DMSO	28.2	25.5

Table 2. *Torsion Angles ϕ, ψ, and ω of the Backbone of Compounds* **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** *in the Crystal* (Amino Acid (*i*) = Gly(1))



	8a	(*S*,*S*)-**8e**	**8f**	(*R*,*S*,*S*)-**8g**	*R*,*S*)-**8h**	**10**
$\phi_{(i)}$	53.7(2)	–96.3(3)	–88.7(5)	70.6(5)	64(1); 62(1)	82.2(6)
$\psi_{(i)}$	32.4(2)	–5.6(5)	–33.9(6)	179.0(4)	–170.3(7); –172.3(7)	155.3(5)
$\omega_{(i)}$	–178.7(1)	173.2(3)	178.7(4)	179.4(4)	175.1(7); 177.9(7)	–169.2(4)
$\phi_{(i+1)}$	55.8(2)	53.9(4)	49.4(6)	–49.6(5)	–51.5(9); –51.0(9)	–53.8(6)
$\psi_{(i+1)}$	21.8(2)	34.3(5)	42.2(6)	–43.4(5)	–36(1); –40.5(9)	–37.8(6)
$\omega_{(i+1)}$	–178.7(1)	179.5(3)	173.1(4)	–173.7(4)	–178.9(7); –177.8(6)	–176.9(4)
$\phi_{(i+2)}$	51.9(2)	61.3(5)	61.3(6)	–66.2(5)	–55 (1); –57(1)	–61.2(6)
$\psi_{(i+2)}$	29.6(2)	13.5(5)	29.4(6)	–13.6(6)	–30(1); –30 (1)	–31.7(6)
$\omega_{(i+2)}$	178.6(1)	–170.8(3)	–177.5(4)	171.5(4)	–179.0(7); –178.1(7)	178.7(4)
$\phi_{(i+3)}$	57.0(2)	55.8(4)	59.4(6)	–55.6(5)	–64.8(9); –58.4(9)	–54.1(7)
$\psi_{(i+3)}$	30.4(2)	30.6(5)	32.4(6)	–32.0(5)	–30(1); –32.6(9)	–39.5(5)
$\omega_{(i+3)}$	166.3(1)	163.6(4)	–170.7(4)	–172.5(4)	–162.1(8); –154.6(7)	175.4(4)
$\phi_{(i+4)}$	–83.0(2)	–81.0(5)	–47.4(7)	–111.0(5)	–57(1); –52(1)	49.4(6)
$\psi_{(i+4)}$	162.8(1)	–179.1(4)	–57.4(7)	179.4(4)	–50(1); –54(1)	45.2(6)

Table 3. *Intramolecular H-Bonds of Compounds* **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (atom numbering refers to *Figs. 1 – 7*)

Compound	N(1)–H···O(8)		N(4)–H···O(11)		N(7)–H···O(14)	
	N···O (Å)	N–H···O (°)	N···O (Å)	N–H···O (Å)	N···O (Å)	N–H···O (Å)
8a	2.928(2)	163(2)	3.052(2)	171(2)	3.013(2)	166(1)
(S,S)-**8e**	3.007(4)	165(4)	2.872(4)	166(4)	-	
8f	2.976(5)	130	2.977(5)	141	-	
(*R*,*S*,*S*)-**8g**	2.960(5)	162(4)	3.001(5)	161(4)	-	
(*R*,*S*)-**8h**	2.974(8)	163;	3.036(8)	149;	-	
	3.055(7)	168	3.067(8)	147		
10	3.034(5)	126	3.000(5)	140	-	

Table 4. *Crystallographic Data for Compounds* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10**

		6a	**8a**	(*S*,*S*)-**8e**
Crystallized from		CH_2Cl_2/Et_2O/hexane	CH_2Cl_2/hexane	AcOEt/hexane
Empirical formula		$C_{35}H_{43}N_5O_6 \cdot 0.5C_6H_{14}$	$C_{31}H_{41}N_5O_8$	$C_{36}H_{43}N_5O_8 \cdot H_2O$
Formula weight		672.84	611.69	691.78
Crystal color, habit		colorless, prism	colorless, prism	colorless, irregular prism
Crystal dimensions [mm]		0.23 × 0.25 × 0.45	0.33 × 0.41 × 0.43	0.25 × 0.27 × 0.50
Temperature [K]		173(1)	173(1)	173(1)
Crystal system		monoclinic	monoclinic	orthorhombic
Space group		$P2_1/n$	$P2_1/n$	$P2_12_12_1$
Z		4	4	4
Reflections for cell determination		22	25	25
2θ range for cell determination [°]		32–39	38–40	23–33
Unit cell parameters	a [Å]	11.642(3)	13.698(3)	15.347(4)
	b [Å]	15.135(3)	13.979(4)	24.232(4)
	c [Å]	21.307(2)	17.409(3)	10.028(4)
	α [°]	90	90	90
	β [°]	97.294(12)	109.133(14)	90
	γ [°]	90	90	90
	V [Å^3]	3724(1)	3150(1)	3729(2)
D_X [g cm^{-3}]		1.200	1.290	1.232
μ(MoK_α) [mm^{-1}]		0.817	0.0940	0.0892
Scan type		$\omega/2\theta$	$\omega/2\theta$	ω
$2\theta_{(max)}$ [°]		55	60	55
Transmission factors (min; max)		-	-	-
Total reflections measured		9296	9898	5535
Symmetry independent reflections		8539	9182	5389
Reflections used [$I > 2\sigma(I)$]		4362	6222	3892
Parameters refined; restraints		484; 164	423; 0	548; 202
Final $R(F)$ [$I > 2\sigma(I)$ reflections]		0.0577	0.0454	0.0549
$wR(F^2)$ (all data)		0.1671	0.1262	0.1682
Weighting parameter (a; b)[a]		0.0830; 0	0.0525; 0.4262	0.0886; 0.8267
Secondary extinction coefficient		0.0022(6)	-	-
Goodness of fit		0.927	1.034	1.058
Final Δ_{max}/σ		0.000	0.000	0.000
$\Delta\rho$ (max; min) [e Å^{-3}]		0.29; –0.24	0.37; –0.18	0.79; –0.26

[a]) $w^{-1} = \sigma^2 (F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$

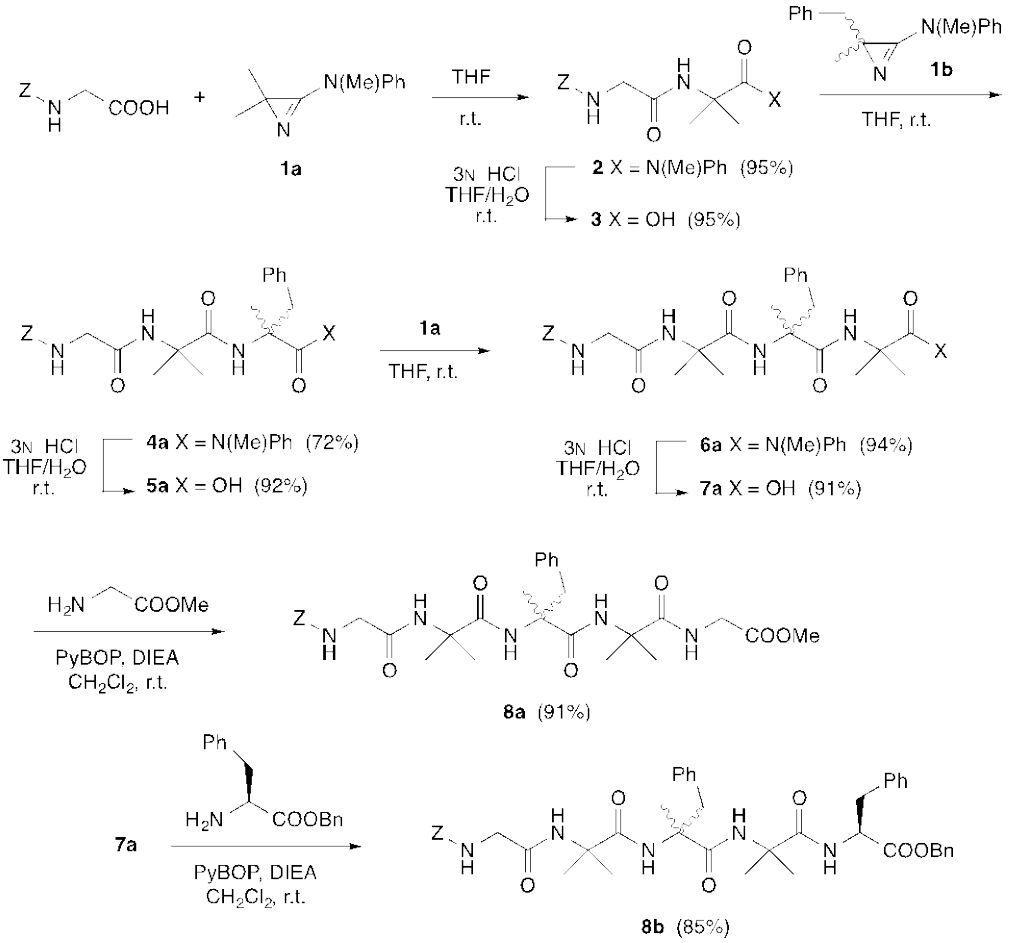
Table 4. *Crystallographic Data for Compounds* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (continued)

		8f	(*R*,*S*,*S*)-**8g**	(*R*,*S*)-**8h**
Crystallized from		AcOEt/hexane	MeOH/AcOEt	AcOEt/MeOH/hexane
Empirical formula		$C_{37}H_{46}N_6O_7 \cdot 0.33C_6H_{14}$	$C_{39}H_{47}N_5O_8 \cdot C_4H_8O_2 \cdot 0.5H_2O$	$C_{40}H_{50}N_6O_7 \cdot 0.5C_6H_{14} \cdot 0.25H_2O$
Formula weight		715.33	810.94	774.46
Crystal color, habit		colorless, plate	colorless, plate	colorless, hexagonal prism
Crystal dimensions [mm]		0.10 × 0.38 × 0.42	0.20 × 0.45 × 0.50	0.36 × 0.36 × 0.38
Temperature [K]		173(1)	173(1)	173(1)
Crystal system		orthorhombic	orthorhombic	trigonal
Space group		*Pbca*	$P2_12_12_1$	$P3_121$
Z		8	4	12
Reflections for cell determination		25	25	25
2θ range for cell determination [°]		21–25	24–35	20–27
Unit cell parameters	*a* [Å]	25.465(4)	16.601(5)	15.706(6)
	b [Å]	20.729(6)	26.785(8)	15.706(6)
	c [Å]	14.536(5)	9.720(6)	60.971(6)
	α [°]	90	90	90
	β [°]	90	90	90
	γ [°]	90	90	120
	V [Å^3]	7673(4)	4322(3)	13026(11)
D_x [g cm^{-3}]		1.239	1.246	1.185
μ(MoK_α) [mm^{-1}]		0.0860	0.0895	0.0813
Scan type		ω	ω	ω
$2\theta_{(max)}$ [°]		50	50	50
Transmission factors (min; max)		0.806; 1.000	0.903; 1.000	-
Total reflections measured		8431	5016	29374
Symmetry independent reflections		6768	4874	15416
Reflections used [$I > 2\sigma(I)$]		2204	3299	8853
Parameters refined; restraints		457; 0	554; 0	1087; 187
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0701	0.0446	0.0787
	$wR(F^2)$ (all data)	0.1842	0.1104	0.2097
Weighting parameter (a; b)[a]		0.0781; 0	0.0392; 0.9522	0.0641; 16.507
Secondary extinction coefficient		-	-	0.0014(2)
Goodness of fit		0.790	1.013	1.057
Final Δ_{max}/σ		0.000	0.000	0.002
$\Delta\rho$ (max; min) [e Å^{-3}]		0.32; –0.25	0.19; –0.21	0.42; –0.38

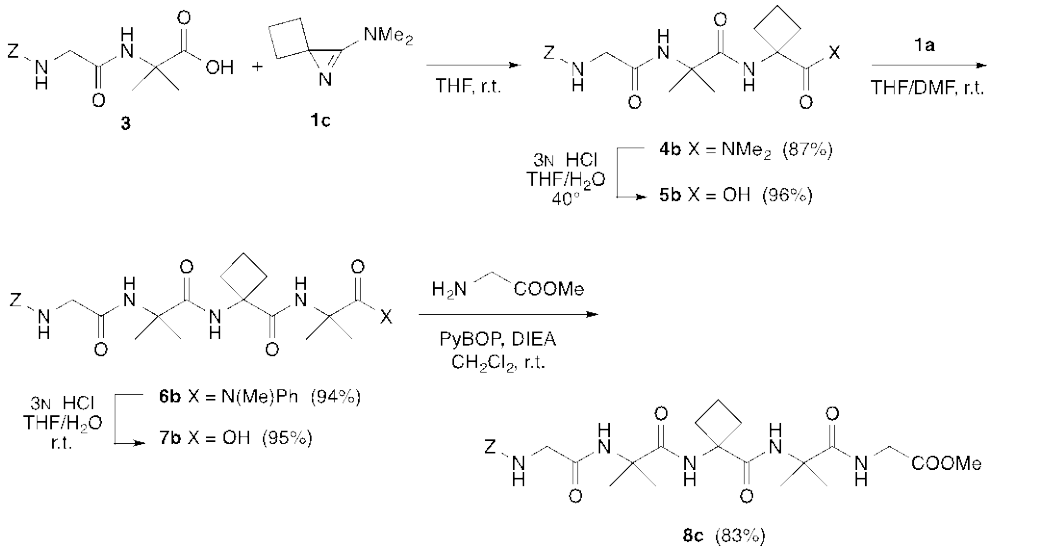
Table 4. *Crystallographic Data for Compounds* **6a**, **8a**, (*S*,*S*)-**8e**, **8f**, (*R*,*S*,*S*)-**8g**, (*R*,*S*)-**8h**, and **10** (continued)

		10
Crystallized from		MeOH
Empirical formula		$C_{27}H_{39}N_5O_8 \cdot CH_4O$
Formula weight		593.67
Crystal color, habit		colorless, prism
Crystal dimensions [mm]		0.18 × 0.33 × 0.50
Temperature [K]		173(1)
Crystal system		orthorhombic
Space group		$P2_12_12_1$
Z		4
Reflections for cell determination		17
2θ range for cell determination [°]		20–26
Unit cell parameters	a [Å]	12.983(9)
	b [Å]	10.249(5)
	c [Å]	23.918(7)
	α [°]	90
	β [°]	90
	γ [°]	90
	V [Å^3]	3183(3)
D_x [g cm^{-3}]		1.239
μ(MoK_α) [mm^{-1}]		0.0928
Scan type		$\omega/2\theta$
$2\theta_{(max)}$ [°]		55
Transmission factors (min; max)		-
Total reflections measured		4118
Symmetry independent reflections		4090
Reflections used [$I > 2\sigma(I)$]		2798
Parameters refined; restraints		407; 36
Final $R(F)$ [$I > 2\sigma(I)$ reflections]		0.0611
$wR(F^2)$ (all data)		0.1975
Weighting parameter (a; b)[a]		0.0808; 2.3471
Secondary extinction coefficient		-
Goodness of fit		1.085
Final Δ_{max}/σ		0.000
$\Delta\rho$ (max; min) [e Å^{-3}]		0.33; –0.36

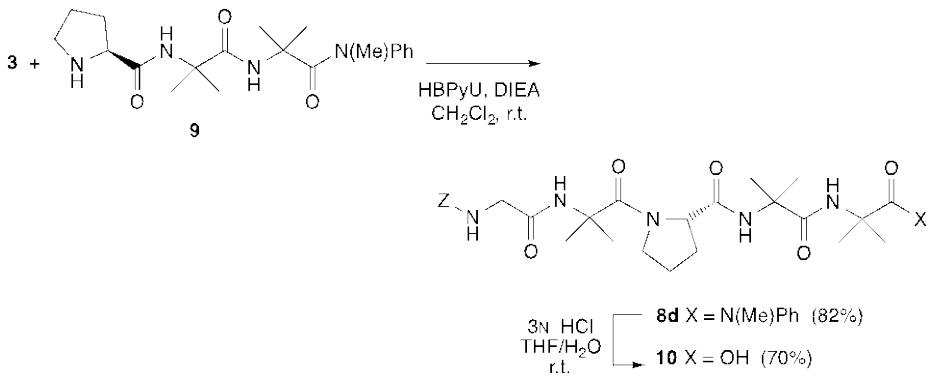
Scheme 1



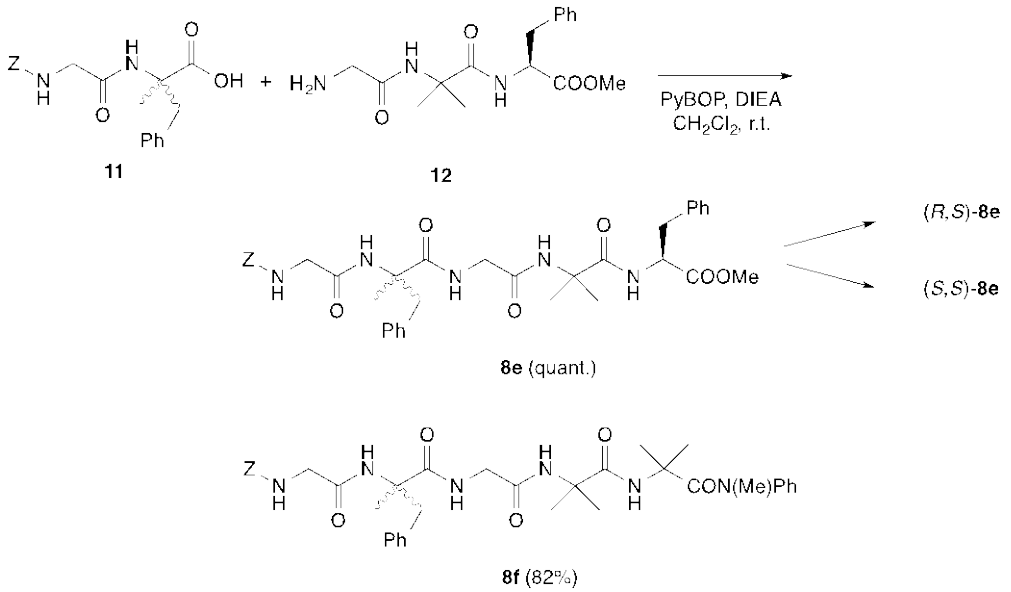
Scheme 2



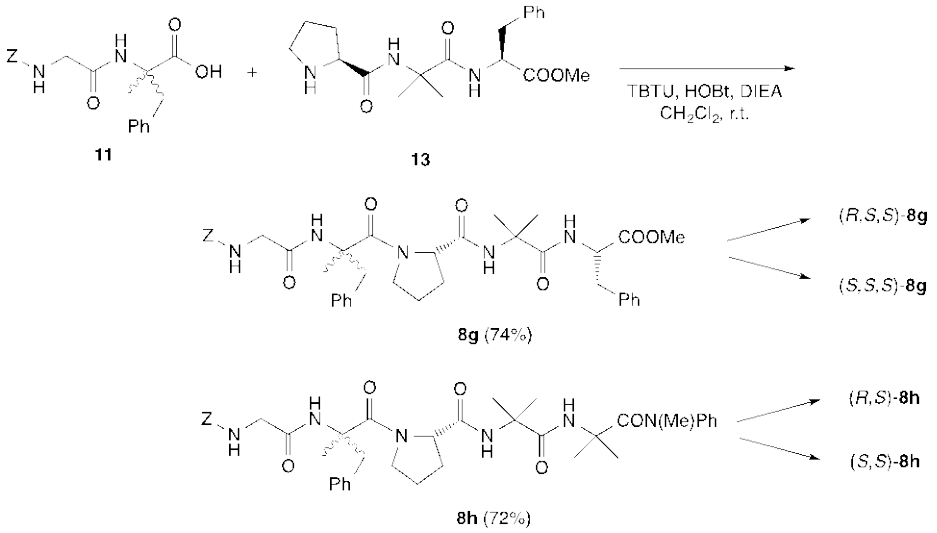
Scheme 3



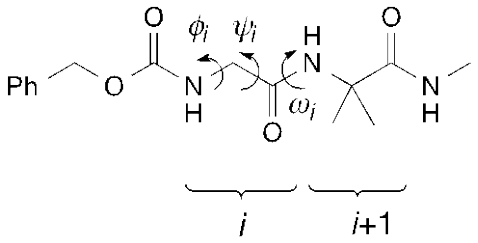
Scheme 4



Scheme 5



Formula for Table 2



Graphical Abstract

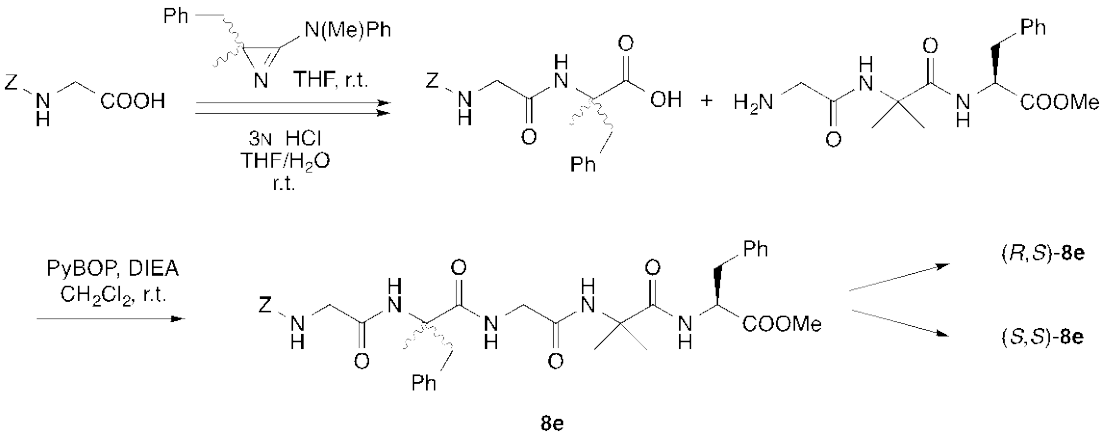


Figure 1

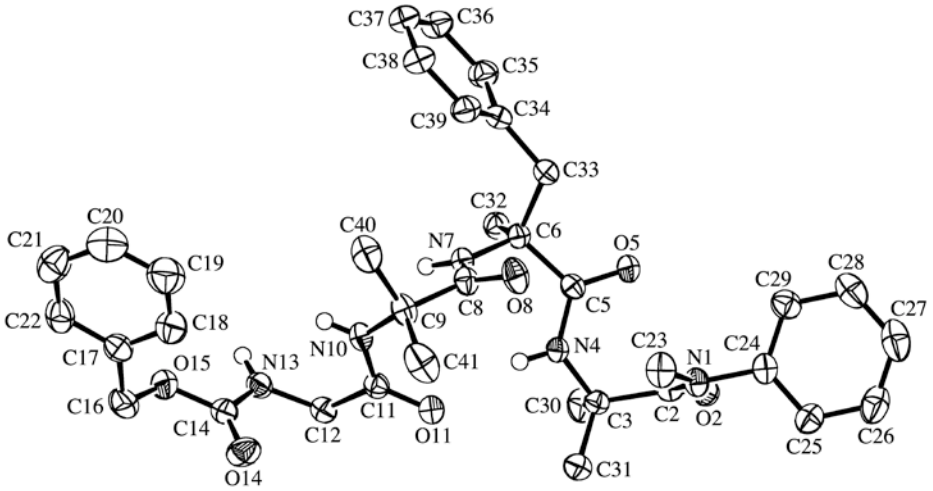


Figure 2

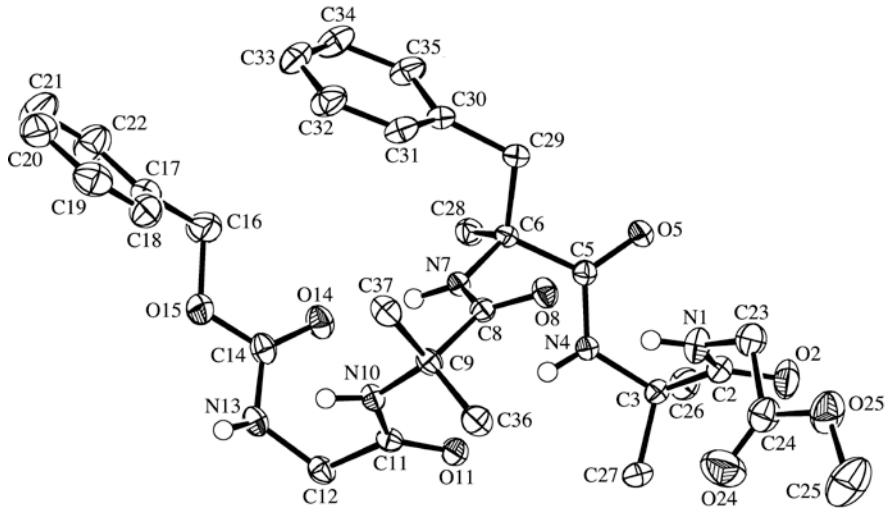


Figure 3

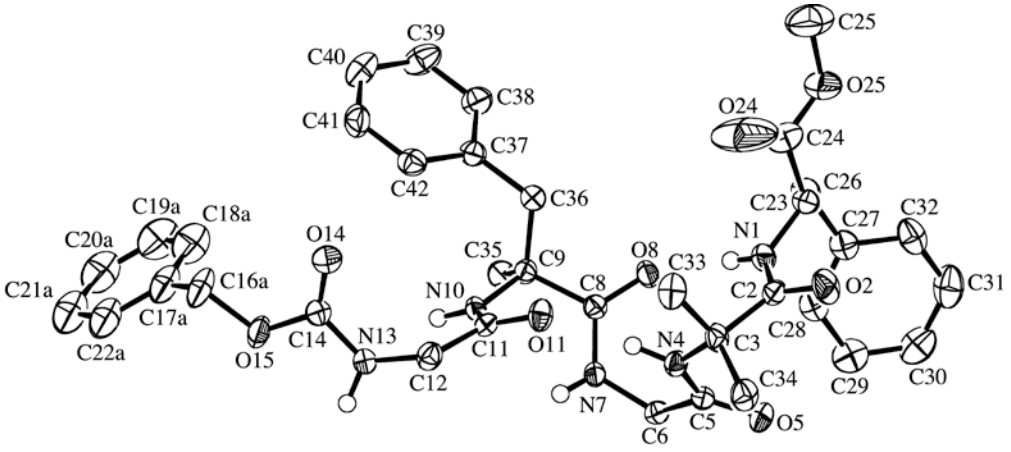


Figure 4

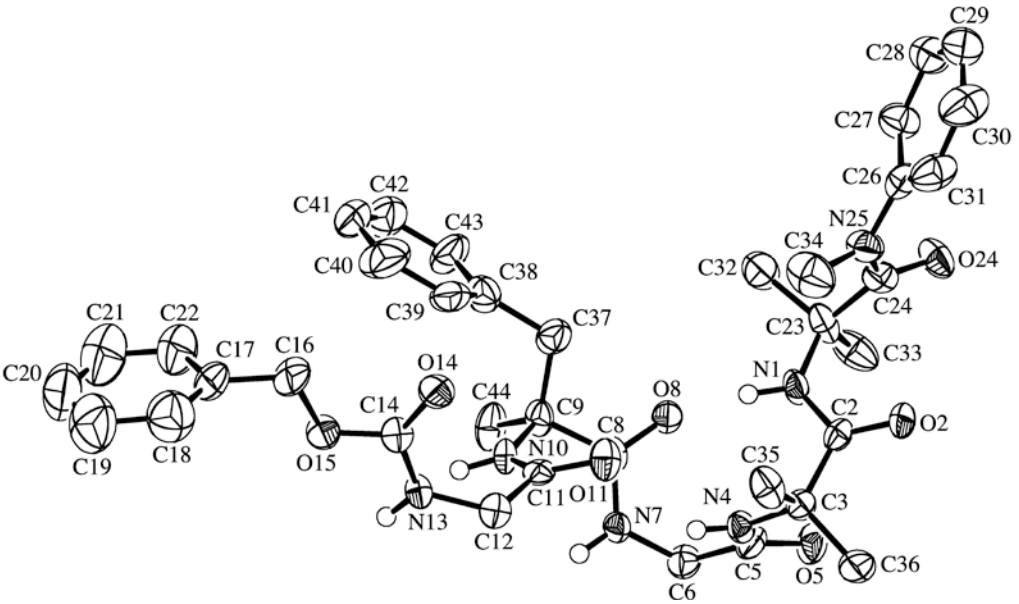


Figure 5

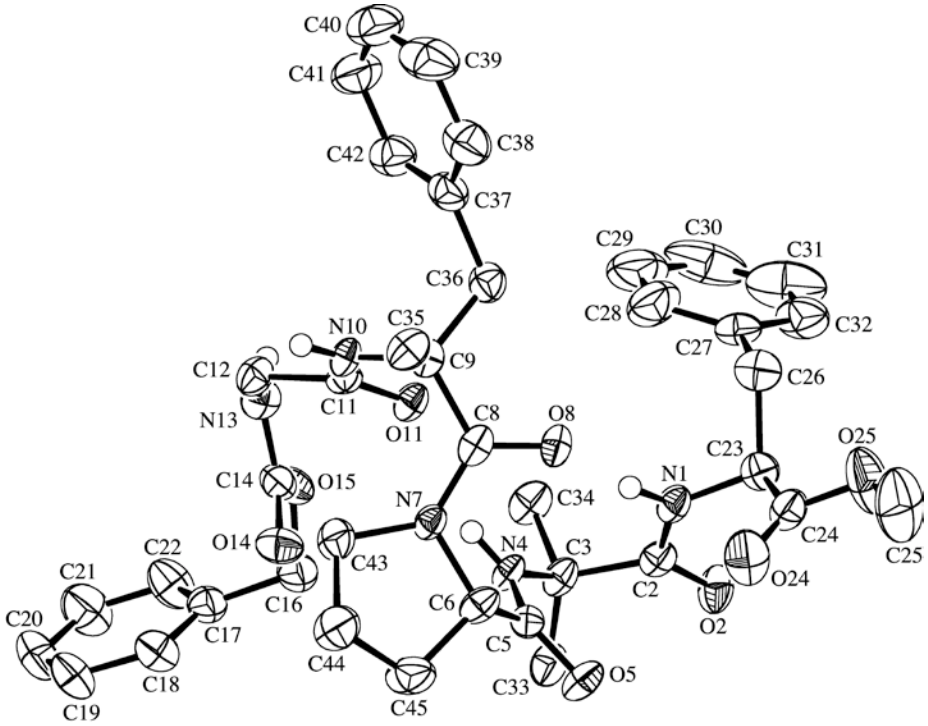


Figure 6

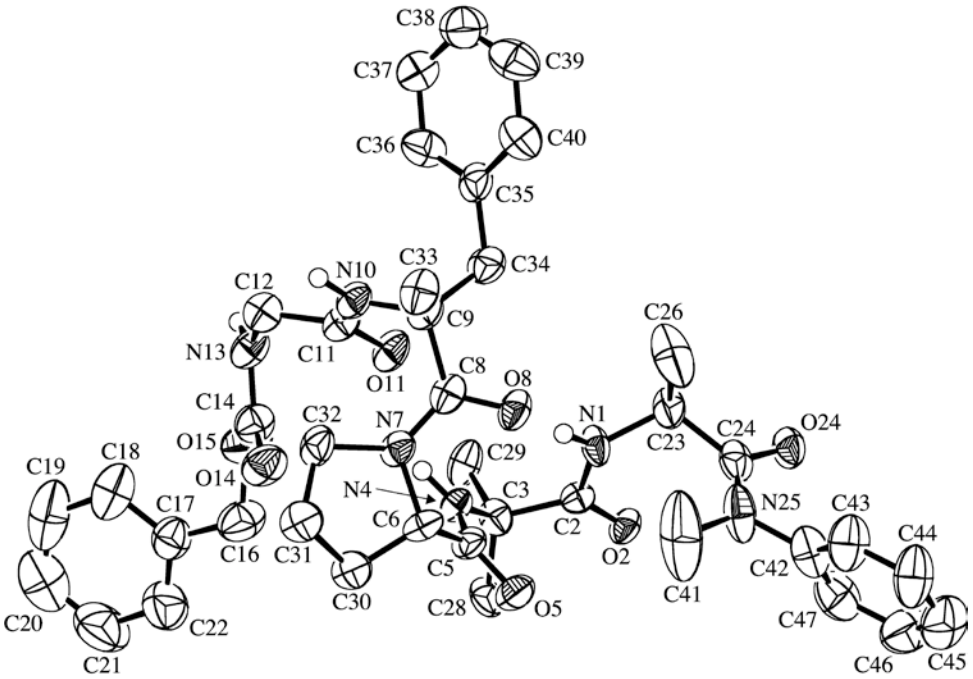
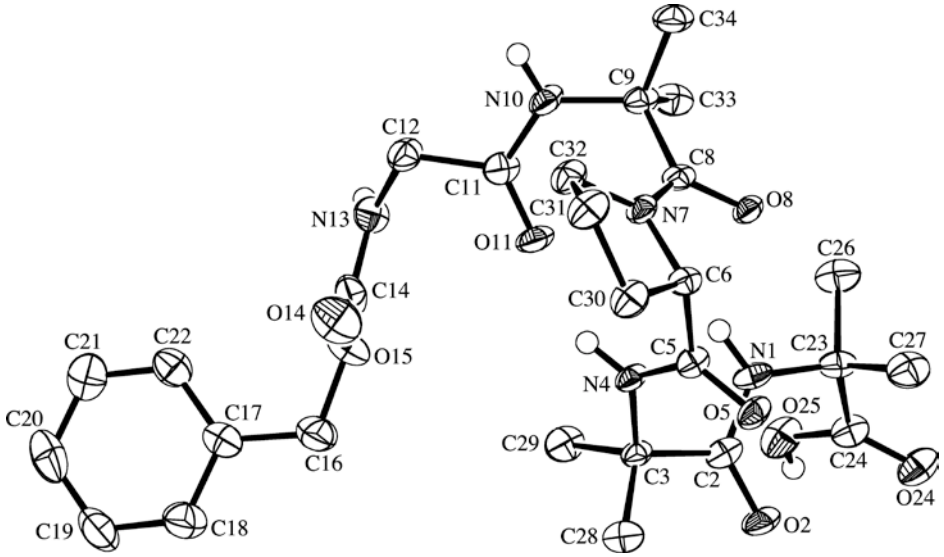


Figure 7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